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VIRUS STUDIES IN HUMANS AND OTHER PRIMATES

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. PROTEIN KINASE ACTIVITY ASSOCIATED WITH EPSTEIN-BARR VIRUS-DETERMINED NUCLEAR ANTIGEN.

Kamata T, Takaki K, Hinuma Y, Watanabe Y
Dept. Molecular Biology, Tokai Univ., Sch. Medicine, Bohseidai, Isehara, Kanagawa-ken, (259-11), Japan
Virology; 113(2):512-520 1981

A cyclic AMP-independent protein kinase activity was found associated with Epstein-Barr virus-determined nuclear antigen (EBNA). The specific activity of protein kinase (casein

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as substrate) rose concurrently with the rise in specific activity of CF activity for EBNA during a series of chromatographic purifications on (1) Sephadex G-200, (2) DNA-cellulose, (3) DEAE-Sephadex A-50, and (4) heparin-Sepharose (or blue sepharose instead of 3 and 4). The kinase activity contained in EBNA thus obtained (about 50% pure as determined by gel electrophoresis) could be immunoprecipitated almost quantitatively with anti-EBNA-positive IgG but not with negative IgG. This kinase immunoprecipitable with antibody to EBNA was detected only in Raji cells and not in EBNA-negative lymphoblastoids, RAMOS cells, or BJAB cells. The EBNA-associated kinase in the immunoprecipitate was unable to phosphorylate exogenous casein efficiently. The analysis for in vitro phosphorylated products in the immunoprecipitate by gel electrophoresis showed that EBNA itself was phosphorylated at serine and threonine residues. (Author abstract) (24 Refs)

2. NONSTRUCTURAL PROTEINS OF HERPES SIMPLEX VIRUS. II. MAJOR VIRUS-SPECIFIC DNA-BINDING PROTEIN.

Powell KL, Littler E, Purifoy DJ
Dept. Microbiology, Univ. Leeds, Leeds LS2 9JT, England
J Virol; 39(3):894-902 1981

The major herpes simplex virus Type 2 DNA-binding infected cell-specific polypeptides 11 and 12 have been purified to homogeneity from extracts of virus-infected cells. Monospecific antiserum to the purified protein has been made and used to examine virus temperature-sensitive mutants for defects in the synthesis of the protein and to probe virus DNA synthesis in isolated chromatin. The purified protein acted directly on a polydeoxyadenylic acid-polydeoxythymidylic acid helix, reducing its melting temperature. The results indicated that the protein functions in virus DNA synthesis. (Author abstract) (24 Refs)

3. HERPES SIMPLEX VIRUS TYPE I DNA POLYMERASE. KINETIC PROPERTIES OF THE ASSOCIATED 3'-5' EXONUCLEASE ACTIVITY AND ITS ROLE IN ARAAMP INCORPORATION.

Derse D, Cheng YC
Dept. Pharmacology and Medicine, Sch. Medicine, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, 27514
J Biol Chem; 256(16):8525-8530 1981

An exonuclease activity copurified with herpes simplex virus type I (HSV-1) DNA polymerase through DNA-cellulose column chromatography and comigrated with DNA polymerase activity on nondenaturing gel electrophoresis at varied polyacrylamide concentrations. A gapped duplex DNA was the preferred substrate for this exonuclease activity since the hydrolytic activity on this type of DNA was much greater than the hydrolysis of either native or heat-denatured DNA. Using 3'-terminally labeled activated calf thymus DNA as substrate, the exonuclease activity was found to be activated by salt and spermidine in a manner identical with HSV-1 DNA polymerase. This activation was accompanied by increases in apparent Km and Vmax values of the activated DNA substrate. Phosphonoformic acid inhibited both DNA polymerase and exonuclease activities uncompetitively with respect to activated DNA and had a Ki of 2.4 uM at an ionic strength of 0.25 u. Of the nucleoside 5'-monophosphates tested only the purine ribonucleotides inhibited the exonuclease activity. The inhibition was noncompetitive with respect to DNA, and GMP was about twice as potent as AMP or IMP. 9-beta-D-arabinosyladenine 5'-monophosphate (araAMP) could be incorporated into DNA by HSV-1 DNA polymerase; however, 9-beta-D-arabinosyladenine 5'-triphosphate would not replace dATP in supporting in vitro HSV-1 DNA synthesis. AraAMP incorporated into primer termini caused a significant decrease in the rate of subsequent primer elongation. These 3'-terminal araAMP residues could be removed by the HSV-1 DNA polymerase-associated exonuclease activity in a manner dependent on GMP concentration. (Author abstract) (21 Refs)

4. DISULFIDE BONDS PROTECT THE ENCAPSIDATED CHROMOSOMES OF SIMIAN VIRUS 40.

Ng SC, Bina M
Dept. Chemistry, Div. Biochemistry, Purdue Univ., West Lafayette, IN, 47906
FEBS Lett; 130(1):47-49 1981

To study the role of disulfide bridges in the protection of encapsidated simian virus 40 (SV40) DNA, the accessibility of viral DNA to micrococcal nuclease (MN) in the presence or absence of reducing agent dithiothreitol (DTT) was tested. Incubation of SV40 virions with increasing concentrations of MN in 5 milliM (mM) calcium chloride did not result in the cleavage of viral DNA. Incubation of SV40 virions with DTT and subsequent treatment with MN and calcium chloride (greater than 1 mM) resulted in digestion of viral DNA. Calcium chloride was only required for the activation of MN. Fractionation on the isokinetic sucrose gradients showed that the digested particles sedimented similarly to the intact virions. Since SV40 wirions do not contain histones H1 or H5, it was concluded that specific types of interactions mediated by divalent ions, protein-protein and protein-DNA prevent the release of nucleosome cores generated by the action of MN on DTT-treated virions. (16 Refs)

5. STABLE ASSOCIATION OF VIRAL PROTEIN VP1 WITH SIMIAN VIRUS 40 DNA.

Brady JN, Lavialle CA, Radonovich MF, Salzman NP
Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
J Virol; 39(2):432-437 1981

Mild dissociation of simian virus 40 particles releases a 110S virion core nucleoprotein complex containing histones and the three viral proteins VP1, VP2, and VP3. The association of viral protein VP1 within this nucleoprotein complex is mediated at least partially through a strong interaction with the viral DNA. Treatment of the virion-derived 110S nucleoprotein complex with 0.25% Sarkosyl dissociated VP2, VP3, and histones, leaving a stable VP1-DNA complex. The VP1-DNA complex had a sedimentation value of 30S and a density of 1.460 g/cc. The calculated mol wt of the complex was 7.9 X 10(6), wit h an av of 100 VP1 molecules per DNA. Agarose gel electrophoresis of the VP1-DNA complex demonstrated that VP1 is associated not only with form I and form II simian virus 40 DNAs but also with form III simian virus 40 DNA generated by cleavage with EcoRI. (Author abstract) (15 Refs)

6. SV40 GENE EXPRESSION IS MODULATED BY THE COOPERATIVE BINDING OF T ANTIGEN TO DNA.

Myers RM, Rio DC, Robbins AK, Tjian R
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
Cell; 25(2):373-384 1981

We analyzed the DNA binding properties of wild-type simian virus 40 large T antigen and found that the protein binds cooperatively to three tandem sites at a regulatory region of SV40 DNA. One consequence of this T antigen: DNA interaction is the specific repression of SV40 early RNA synthesis in vitro. We mapped a region of 85 base pairs that is necessary and sufficient to initiate early SV40 transcription in vitro. This promoter region lies directly adjacent to the third T antigen binding site but does not include the 'TATA' sequence. To determine how T antigen interacts with its binding sites to repress RNA synthesis, we analyzed transcription directed by a variety of wild-type, mutant and hybrid template DNAs. Our findings suggest that the cooperative binding of T antigen to its sites is directly responsible for inhibiting the initiation, rather than blocking elongation, of early RNA synthesis. A model is presented to explain the role of T antigen binding in the regulation of viral transcription and DNA replication during SV40 lytic infection. (Author abstract) (68 Refs)

7. CORONAVIRUS-ASSOCIATED ANTIBODIES IN NASOPHARYNGEAL CARCINOMA AND INFECTIOUS MONONUCLEOSIS.

Arnold W, Klein M, Wang JB, Schmidt WAK, Trampisch HJ

Dept. Otorhinolaryngology, Klinikum Grosshadern, Marchioninstrasse 15, D-8000 Munich 70, W. Germany

Arch Otorhinolaryngol (NY); 232(2):165-177 1981

Particles in the cytoplasm of nasopharyngeal carcinoma (NPC) cells were found which resembled coronaviruses. To determine the nature of these particles serum titer determinations were performed in NPC patients, infectious mononucleosis patients, and a control group. Epstein-Barr nuclear antigen (EBNA) test were made on tumor cells from NPC tissues and cells from cultures infected with coronaviruses. For immunological identification of coronavirus, the human coronavirus strain 229E was cultured on human fetal lung fibroblast MRC-C cells. Comparison of antibody levels showed clearly higher levels of IgG in NPC patients than in controls. IgA was the same in either group. IgM titer was in the low range in NPC patients. Infectious mononucleosis patients showed similar tiers to the NPC patients. The EBNA test was positive in all NPC cells, negative in cell cultures infected with coronavirus. In immunofluorescence tests serum from NPC patients produced intense fluorescence when applied to coronavirus-infected cells. Known high-titer coronavirus sera did not produce a similar result in MRC cells not infected with coronavirus. Evidently coronaviruses are present in the cytoplasm of NPC tumor cells. A correlation between the RNA coronavirus and the Epstein-Barr virus suggests a possible interaction between them as a factor in NPC. (35 Refs)

8. STRUCTURAL CHARACTERIZATION OF THE MAJOR INTERNAL PROTEIN OF THE SKA 21-3 VIRUS. BRIEF REPORT.

Brouwer J, Den Dulk J

Pathology Lab., State Univ. Leiden, Wassenaarseweg 62, 2333 Al Leiden, The Netherlands

Arch Virol; 69(1):85-90 1981

The major internal protein of the putative human type C virus SKA21-3 was compared with homologous proteins of mammalian type C viruses by two-dimensional analyses of radioiodinated tryptic peptides. The SKA21-3 virus protein displayed the same pattern as the protein of simian sarcoma virus. (Author abstract) (15 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

9. ENHANCEMENT OF EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LYMPHOCYTES BY TELEOCIDIN.

Hoshino H, Miwa M, Fujiki H, Sugimura T, Yamamoto H, Katsuki T, Hinuma Y

Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan

Cancer Lett; 13(4):275-280 1981

The effect of teleocidin and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on Epstein-Barr virus (EBV)-induced transformation in human lymphocytes was examined. Human umbilical cord lymphocytes were infected with the B95-8 strain of EBV and cultured in soft agar. Teleocidin enhanced colony-forming efficiency approx 5x at 0.1 nanog/ml. TPA had a similar but lesser effect at the same concentration. Optimal concentrations were, respectively, 2.2 and 1.6 x 10(-10) M. Using the P3HR-1 EBV strain, which unlike strain B95-8 induces early antigen (EA) in C-6 lymphoblastoid cells after superinfection, the effects on plating efficiency were tested. The number of EA-positive cells as detected by immunofluorescence increased 2-3x in the presence of teleocidin or TPA. Cultures not infected with P3HR-1 produced less than 1% EA-positive cells even with teleocidin or TPA. Colony-forming efficiency of the newly transformed lymphoblastoid cells was 2x as great in the presence of 0.5 nanog/ml teleocidin as in its absence. TPA is known to have a similar effect. The evidence suggests that teleocidin and TPA act similarly to enhance the efficiency of EBV infection of cord blood lymphocytes and also to stimulate colony formation of lymphocytes newly transformed by EBV. (19 Refs)

10. CHARACTERISTICS OF EPSTEIN-BARR VIRUS ACTIVATION OF HUMAN B LYMPHOCYTES.

Bird AG, Britton S, Ernberg I, Nilsson K

(c/o Britton) Dept. Immunobiology, Wallenberg Lab., 10405 Stockholm 50, Sweden

J Exp Med; 154(3):832-839 1981

The correlation between the induction of viral antigens, de novo synthesis of cellular DNA, and immunoglobulin (Ig) secretion of in vitro Epstein-Barr virus (EBV)-infected B lymphocytes was studied. The induction of IgM-secreting cells and of DNA synthesis fell linearly as a function of B95-8 EBV dilution for highly purified B cells incubated with B95-8 EBV. The role of de novo DNA synthesis and transformation in the EBV-dependent induction of Ig secretion was studied. In comparing the EBV responsiveness of purified (B) vs nonpurified (B plus T lymphocytes), the kinetics of response was measured by the development of IgM-secreting cells. T cell-derived preparations showed a continuous increase of cells producing IgM, as well as a high proportion of Epstein-Barr nuclear antigen (EBNA)-positive cells as late as 14 days after initiating the culture, at a time when cell mixtures containing T cells showed very few Ig-secreting cells, as well as a low content of EBNA-positive cells. The results indicated that the EBV-induced activation of human B lymphocytes is a dose-dependent, one-hit phenomenon, and that the maturational step involved in the process of activation requires de novo DNA synthesis. (21 Refs)

11. THE SPONTANEOUS AND INDUCED SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN RAJI CELLS IMMOBILIZED ON SURFACES COATED WITH ANTI-LYMPHOCYTE GLOBULIN.

Bayliss GJ, Wolf H

Max von Pettenkofer Inst., Pettenkoferstrasse 9a, 8000 Munich 2, W. Germany

J Gen Virol; 54(part2):397-401 1981

Immobilization of Raji cells on surfaces coated with anti-lymphocyte globulin (ALG) at low densities lead to the synthesis of Epstein-Barr virus (EBV) early antigen (EA) in up to 5% of the cells. At higher cell densities the percentage of antigen-positive cells decreased and at confluency no antigen synthesis was observed. Addition of iododeoxyuridine (IdUrd) to low density cultures increased the expression of EA to 20%, whereas in confluent cultures the cells could not be induced to synthesize EA. Treatment of cells in suspension with ALG failed to induce EA synthesis and did not potentiate the effect of IdUrd. Immobilized Raji cells proved to be suitable targets for superinfection with EBV derived from P3HR1 cultures. (Author abstract) (11 Refs)

12. SYNTHESIS OF VIRUS-SPECIFIC PROTEINS IN SIMIAN SARCOMA VIRUS-TRANSFORMED PRIMATE CELLS.

Bergholz CM

Paper Product Div., Human Safety Support, Proctor and Gamble Co., 6100 Center Hill Road, Cincinnati, OH, 45224

Virology; 114(1):113-123 1981

Marmoset monkey cells productively and nonproductively transformed by simian sarcoma virus (SSV) were evaluated for expression of simian sarcoma associated virus (SSAV)-specific structural polypeptides and SSV transformation-specific polypeptides. Virus-producing cells contained, in addition to virus structural proteins, a 62,000-dalton polypeptide (pr62 gag) precipitable by antisera specific for SSAV p28 or p10, and a polypeptide of approx 80,000 daltons (pr80env) which could be glucosamine-labeled and which was precipitated by antisera specific for SSAV envelope proteins. Results of pulse-chase experiments provided evidence for a precursor-product relationship between pr62 gag and p28 and between pr80 env and the envelope proteins gp70, p15E, and p12E. Pr62 and p12 were the only detectable phosphorylated virus-specific polypeptides. Nucleic acid hybridization techniques demonstrated SSAV-related DNA and RNA in clonal SSV-transformed nonproducer marmoset cell lines (HF/SSV-NP), but synthesis of SSAV-related protein was demonstrated in only one of five of these lines. This cell line expressed pr62 which was not processed to yield p28 or other gag gene products. Gel electrophoresis of immunoprecipitates demonstrated that SSV does not express a transformation-specific polyprotein comprised in part of either p28, p10, or p12 and a nonstructural component. Antibodies which precipitated a protein specific for SSV-transformed cells were not detected in sera from marmoset monkeys bearing SSV-induced tumors, or in sera from a goat or marmosets inoculated with autologous SSV-transformed cells or HF/SSV-NP cells. (Author abstract) (33 Refs)

13. HUMAN FETAL BRAIN CELLS IN CULTURE. INCREASE IN GM2 GANGLIOSIDE AFTER SV-40 TRANSFORMATION.

Hoffman LM, Brooks SE, Schneck L

Neuroscience Center, Kingsbrook Jewish Medical Center, Brooklyn, NY, 11203

Biochim Biophys Acta; 665(3):359-361 1981

The composition of gangliosides in a cultured human fetal brain cell line was examined before and after SV-40 transformation. In contrast to most reports on other cell lines, an increase was observed in the complex ganglioside GM2 in the SV-40-transformed brain cell line. (Author abstract) (11 Refs)

14. NONDETECTION OF INFECTIOUS HEPATITIS B VIRUS IN A HUMAN HEPATOMA CELL LINE PRODUCING HEPATITIS B SURFACE ANTIGEN.

Tabor E, Copeland JA, Mann GF, Howard CR, Skelly J, Snoy P, Zuckerman AJ, Gerety RJ

Bureau Biologics, 8800 Rockville Pike, Bethesda, MD, 20205

Intervirology; 15(2):82-86 1981

The PLC/PRF/5 human hepatoma cell line producing hepatitis B surface antigen (HBsAg) was studied to determine whether infectious hepatitis B virus (HBV) was also being produced. Two chimpanzees with no previous exposure to HBV and no serologic markers of past or active HBV infection were inoculated iv with 50 ml of either tissue culture supernatant fluid (357 ng/ml HBsAg) or a suspension of cells disrupted by repeated freeze-thaw cycles (57 ng/ml HBsAg). No evidence of HBV infection was detected in either chimpanzee during 6 mo of evaluation. This study suggests that the expression of a portion of the HBV genome, when a portion or all of that genome has been incorporated in a host cell, can result in the production of HBsAg without infectious HBV. If it becomes possible to produce a similar expression of this portion of the genome by itself in nonmalignant cells, HBsAg without HBV may be produced in vitro for use in hepatitis B vaccines. (Author abstract) (21 Refs)

VIRUS REPLICATION AND EXPRESSION

15. EPSTEIN-BARR VIRUS POLYPEPTIDES: IDENTIFICATION OF EARLY PROTEINS AND THEIR SYNTHESIS AND GLYCOSYLATION.

Feighny RJ, Henry BE, Pagano JS

Cancer Res. Center, Univ. North Carolina at Chapel Hill Sch. Medicine, Chapel Hill, NC, 27514

J Virol; 39(2):651-655 1981

We have identified at least six early polypeptides induced by Epstein-Barr virus in cells or under conditions which are nonpermissive for Epstein-Barr virus DNA replication ranging in mol wt from 140,000 to 26,000. (Author abstract) (18 Refs)

16. REPLICATION OF SIMIAN VIRUS 40 DNA IN NORMAL HUMAN FIBROBLASTS AND IN FIBROBLASTS FROM XERODERMA PIGMENTOSUM.

Ozer HL, Slater ML, Dermody JJ, Mandel M
Dept. Biological Sciences, Hunter Coll., City Univ. New York, New York, NY, 10021
J Virol; 39(2):481-489 1981

Simian virus 40 infection of semipermissive human diploid fibroblasts (HF), at early passage in cell culture, was compared with that of permissive established monkey cell lines. Viral DNA can be readily detected at 24 to 48 hr postinfection at 37 C with a high multiplicity of infection, approaching 10% of that of monkey cells (TC7). The length of time necessary for replication of an av molecule of viral DNA was found to be indistinguishable in HF and TC7 cells. Strand elongation plus termination were assessed by following the accumulation of DNA I at 40 C from replicative intermediates of tsA30 prelabeled at 33 C, obviating isotope pool problems. Combined initiation and elongation of wild-type viral DNA was measured by density shift experiments involving a 5-bromodeoxyuridine chase of prelabeled [3H]thymidine-labeled viral DNA. Determination of accumulation of viral T and V antigens supports the conclusion that the most likely basis for the reduced virus yield in HF cells results from the inefficiency of an early stage in virus infection, before or during uncoating. Similar results were obtained in fibroblasts derived from patients with xeroderma pigmentosum, suggesting that enzymes of uv repair are not required in unirradiated simian virus 40 DNA synthesis. (Author abstract) (34 Refs)

17. MULTIPLICITY-DEPENDENT HOST RANGE RESTRICTION OF HUMAN ADENOVIRUS IN HUMAN EMBRYONAL CARCINOMA CELLS.

Nicolas JC, Levine AJ
(c/o Levine) Dept. Microbiology, State Univ. New York Sch. Medicine, Stony Brook, NY, 11794
Virology; 113(2):787-789 1981

The ability of human adenovirus Type 5 to replicate and produce infectious virus was examined in two different cell lines, HeLa cells and Tera I, a human embryonal carcinoma cell line. High titers of infectious adenovirus were produced (10(9) PFU/ml) by growth in HeLa cell cultures independent of the input multiplicity of infection (by 96 hr postinfection). On the other hand, 3-4 logs less infectious virus were synthesized in Tera I cells when low (0.01-0.1 PFU/cell) input multiplicities of infection were used. At input multiplicities of 1, 10, or 100 PFU/cell, 1-1 1/2 logs less infectious virus was produced by Tera I cells than HeLa cell cultures at late times (96-144 hr) postinfection. These results demonstrate an adenovirus input multiplicity-dependent, host range restriction in human embryonal carcinoma cells. These observations may provide a means of examining the differences between cells with distinct developmental potentials. (Author abstract) (20 Refs)

18. PROPAGATION OF B-LYMPHOTROPIC PAPOVAVIRUS (LPV) IN HUMAN B-LYMPHOMA CELLS AND CHARACTERIZATION OF ITS DNA.

Brade L, Vogl W, Gissman L, Zur Hausen H
(c/o Zur Hausen) Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Str. 11, 78 Freiburg, W. Germany
Virology; 114(1):228-235 1981

The B-lymphotropic papovavirus (LPV) isolated originally from African green monkey (AGM) B-lymphoblasts has been adapted to growth in the human Epstein-Barr virus (EBV)-negative B-lymphoma line BJA-B by repeated passages within these cells. After 11 passages of virus approx 20-25% of the cells were infectible within a 6 day period. Except for an abortive infection of another EBV-negative human B-lymphoma line, Ramos, and the EBV-positive Raji line of Burkitt lymphoma origin, cells of all other human lines of lymphatic origin tested thus far proved to be refractory to this infection. Viral DNA isolated from the BJA-B adapted strain was compared to that from the original AGM isolate. Only minor modifications were demonstrable in the HaeIII cleavage pattern of both isolates. A BJA-B subline persistently infected with LPV was established after cocultivation of BJA-B cells with LPV-producing AGM lymphoblasts. About 0.5-15% of these cells synthesized viral antigens at various intervals of cultivation. Viral DNA isolated from these cells after 12 mo of persistent infection revealed a remarkable heterogeneity in size and in the cleavage pattern when analyzed with restriction endonucleases. Molecular cloning of this DNA in pBR 322 plasmid underlined this heterogeneity. The majority of clones obtained revealed deletions which preferentially mapped within the D-F fragments of the HaeIII map. (Author abstract) (21 Refs)

19. NATURAL OCCURRENCE OF DELETION MUTANT OF HUMAN PAPOVAVIRUS BK CAPABLE OF INDUCING T ANTIGEN.

Watanabe S, Yoshiike K, Yuasa Y, Uchida S
Dept. Enteroviruses, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo, 141, Japan
J Gen Virol; 54(part2):431-435 1981

Human papovavirus BK DNA resistant to digestion with EcoRI endonuclease had the capacity to direct synthesis of T antigen in human embryonic kidney cells. The study demonstrated the natural occurrence of defective deletion mutants with intact early functions of the viral genome. (Author abstract) (17 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

20. HERPES SIMPLEX VIRUS TYPE 1 HINDIII FRAGMENT L ENCODES SPLICED AND COMPLEMENTARY MRNA SPECIES.

Frink RJ, Anderson KP, Wagner EK
Dept. Molecular Biology and Biochemistry, Univ. California, Irvine, Irvine, CA, 92717
J Virol; 39(2):559-572 1981

We have used DNA bound to cellulose to isolate and translate in vitro herpes simplex virus Type 1 (HSV-1) mRNA's encoded by HindIII fragment L (mapping between 0.592 and 0.647), an 8,450-base-pair (8.45-kb) portion of the long unique region of the viral genome. Readily detectable, late mRNA's 2.7 and 1.9 kb in size encoding 69,000-and 58,000-dalton polypeptides, respectively, were isolated. A very minor late mRNA family composed of two colinear forms, one 2.6 kb and one 2.8 kb, was isolated and found to encode only an 85,000-dalton polypeptide. A major early mRNA, 1.8 kb in size encoding a 64,000-dalton polypeptide, was also isolated. High-resolution mapping of these mRNA's by using S1 nuclease and exonuclease VII digestion of hybrids between them and 5' and 3' end-labeled DNA fragments from the region indicated that the major early mRNA contained no detectable splices, and about half of its 3' end was complementary to the 3' region of the very minor 2.6-to 2.8-kb mRNA's encoded on the opposite strand. These mRNA's also contained no detectable splices. The major late 2.7-kb mRNA was found to be a family made up of members with no detectable splices and members with variable-length (100 to 300 bases) segments spliced out very near (ca 50 to 100 bases) the 5' end. (Author abstract) (65 Refs)

21. PHYSICAL MAPPING OF DRUG RESISTANCE MUTATIONS DEFINES AN ACTIVE CENTER OF THE HERPES SIMPLEX VIRUS DNA POLYMERASE ENZYME.

Knopf KW, Kaufman ER, Crumpacker C
Medical Res. Council Virology Unit, Univ. Glasgow, Glasgow, Scotland
J Virol; 39(3):746-757 1981

The genome structures of herpes simplex virus Type 1 (HSV-1)/HSV-2 intertypic recombinants have been previously determined by restriction endonuclease analysis, and these recombinants and their parental strains have been employed to demonstrate that mutations within the HSV DNA polymerase locus induce an altered HSV DNA polymerase activity, exhibiting resistant to three inhibitors of DNA polymerase. The viral DNA polymerases induced by two recombinants and their parental strains were purified and shown to possess similar mol wt (142,000 to 144,000) and similar sensitivity to compounds which distingui sh viral and cellular DNA polymerases. The HSV DNA polymerases induced by the resistant recombinant and the resistant parental strain were resistant to inhibition by phosphonoacetic acid, acycloguanosine triphosphate, and the 2',3'-dideoxynucleoside triphosphates. The resistant recombinant (R6-34) induced as much acycloguanosine triphosphate as did the sensitive recombinant (R6-26), but viral DNA synthesis in infected cells and the viral DNA polymerase activity were not inhibited. The 2',3'-dideoxynucleoside-triphosphates were effective competitive inhibitors for the HSV DNA polymerase, and the Ki values for the four 2',3'-dideoxynucleoside triphosphates were determined for the four viral DNA polymerases. The polymerases of the resistant recombinant and the resistant parent possessed a much higher Ki for the 2',3'-dideoxynucleoside triphosphates and for phosphonoacetic acid than did the sensitive strains. A 1.3-kilobase-pair region of HSV-1 DNA within the HSV DNA polymerase locus contained mutations which conferred resistance to three DNA polymerase inhibitors. This region of DNA sequences encoded for an amino acid sequence of 42,000 mol wt and defined an active center of the HSV DNA polymerase enzyme. (Author abstract) (29 Refs)

22. HERPESVIRUS SAIMIRI DNA IN TUMOR CELLS-DELETED SEQUENCES AND SEQUENCE REARRANGEMENTS.

Desrosiers RC
New England Regional Primate Res. Center, Harvard Medical Sch., Southborough, MA, 01772
J Virol; 39(2):497-509 1981

Herpesvirus saimiri DNA in continuous lymphoblastoid cell lines obtained from viral induced tumors in marmosets has been analyzed by gel electrophoresis of restricted DNA, Southern transfer to nitrocellulose filters, and hybridization to 32P-labeled viral DNA or DNA fragments. The viral DNA fragments EcoRI-G, -H, -D, and -I, KpnI-A, and BamHI-D and -E were not detected in Southern transfers of DNA from the nonproducing 1670 cell line. For each restriction endonuclease, a new fragment appeared, consistent with a 13.0-megadalton deletion of viral DNA sequences. This deletion encompassed 35 to 48 +-0.6 megadaltons from the left end of the unique DNA region. A sequence arrangement map is presented for the major population of H saimiri DNA sequences in the 1670 cell line. Although H saimiri DNA in the nonproducing 70N2 cell line can be distinguished from viral DNA in the 1670 cell line by several criteria, the same sequences were found to be deleted in the major population of viral DNA molecules. Unlike 1670 and 70N2 cells, restricted DNA from the virus-producing cell lines 77/5 and 1926 contained all of the DNA fragments present in the parental virion DNA. DNA from 1670, 70N2, and 77/5 cells contained additional viral DNA fragments that did not comigrate with any virion DNA fragments. Most of these unexplained fragments were confined to or highly enriched in partially purified circular or linear DNA fractions. DNA from tumor cells taken directly from a tumor-bearing animal contained viral DNA indistinguishable from the parental virion DNA by the assay conditions used. These results indicate that viral DNA sequence rearrangements can occur upon cultivation of tumor cells in vitro and that excision of DNA sequences from the viral genome may play a role in establishing the nonproducing state of some tumor cell lines. (Author abstract) (15 Refs)

23. HUMAN CYTOMEGALOVIRUS DNA: RESTRICTION ENZYME CLEAVAGE MAPS AND MAP LOCATIONS FOR IMMEDIATE-EARLY, EARLY, AND LATE RNAS.

Demarchi JM

Dept. Microbiology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232

Virology; 114(1):23-28 1981

Complete physical maps for human cytomegalovirus (Davis strain) DNA were constructed from fragments produced by restriction endonucleases HindIII, XbaI, and EcoRI. The results showed that the human cytomegalovirus genome has a structural organization similar to that of the herpes simplex virus genome: a long (L) segment, comprising 82% of the genome, joined to a short (S) segment, comprising the remaining 18% of the genome. Permutations of the S and L segments produce four different molecular arrangements which are represented in equimolar proportions in virion DNA preparations. Heterogeneity in the size of the DNA was detected within fragments which map at one terminus of the S segment and also in fragments which map at one terminus of the L segment. The regions of the genome from which RNA synthesized at various times after infection originates was determined. Immediate-early RNA (RNA synthesized in the presence of cycloheximide) was restricted to a few regions on the genome but hybridized in abundance to a region which mapped between 0.686 and 0.733 units (within the L segment). Early RNA (synthesized in the absence of viral DNA synthesis) hybridized to most areas of the genome, but in particular abundance to a small region which mapped between 0 and 0.046 units (also within the L segment). RNA which accumulated during the late phase of infection was not characterized by particular abundances to any region of the genome. (Author abstract) (33 Refs)

24. INHIBITION OF SV40 REPLICATION IN SIMIAN CELLS BY SPECIFIC PBR322 DNA SEQUENCES.

Lusky M, Botchan M
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Nature; 293(5827):79-81 1981

Dual-host replicons such as a unit consisting of a bacterial plasmid and genes from a mammalian virus could be of considerable utility in cloning specific genes that are properly the part of the mammalian host's genome and in amplifying the expression of specific cloned eukaryotic genes. Such a dual-host replicon exists: SV40-pBR322, which consists of an Escherichia coli plasmid and the SV40 genome, but it replicates poorly after transfection of simian cells and also shows a reduced ability to retransform E coli following isolation after transfection. Initial experiments showed that this recombinant plasmid did not replicate to any significant extent in transfected CV-1 simian cells and replicated far less well than wild type SV40 in COS7 cells (a permissive strain of CV-1). Two types of experiment showed that these results were not due to a lack of normal A gene expression in the recombinant plasmid but rather were likely due to a cis-acting element present in the chimeric molecule: (1) intact SV40 DNA enzymatically excised from the recombinant could replicate like wild type SV40 in both CV-1 and COS7 cells and (2) when a partial head-to-tail tandem duplication of SV40 was transfected into either CV-1 or COS7 cells, excision of genomic length viral DNA occurred leading to accumulation of detectable form I and form II SV40 DNA. Because SV40 replication in simian cells produces defective viral DNA, plasmid progeny extracted from COS7 cells were used to transform E coli cells; the plasmid DNA was purified from the bacterial hosts and examined for molecules with either a selective transforming ability or a higher replication rate in simian cells: restriction analysis revealed 10 such plasmids that had undergone overlapping deletions near the pBR322 origin of replication, 5 of which replicated in both COS7 and CV-1 cells at rates equal to that of authentic SV40 DNA. This result shows that certain pBR322 sequences interfered with SV40 replication in simian cells. The structures of some of these deletions and their genetic consequences are discussed. The molecular basis for the described restrictions is not known. (18 Refs)

25. DELETION MUTANTS OF ADENOVIRUS 2: ISOLATION AND INITIAL CHARACTERIZATION OF VIRUS CARRYING MUTATIONS NEAR THE RIGHT END OF THE VIRAL GENOME.

Challberg SS, Ketner G
(c/o Ketner) Dept. Biology, Johns Hopkins Univ., Baltimore, MD, 21218
Virology; 114(1):196-209 1981

A series of eight deletion mutants of human adenovirus 2 have been isolated by a procedure which employs temperature-sensitive adenovirus mutants as helper viruses. Seven of these deletions are located in the right end of the viral genome and cover portions of early regions three and/or four. The mutant with the largest deletion (807) has been separated from its helper by CsCl density gradient centrifugation. Measurements of the synthesis of viral DNA and late viral protein in 807-infected cells show that the mutant synthesizes DNA normally, and that it produces reduced amounts of some, but not all, late proteins. These observations suggest that while the region 82.5-95 on the adenoviral genome contains no gene essential for DNA replication, it does include a gene or site whose function affects the synthesis of late proteins encoded by widely separated regions of the viral genome. (Author abstract) (47 Refs)

26. THE NATURE OF THE DNA ASSOCIATED WITH INCOMPLETE PARTICLES OF ADENOVIRUS TYPE 2.

Khittoo G, Weber JM
Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544
J Gen Virol; 54(part2):343-355 1981

The nature of the DNA in incomplete particles (IP) synthesized by adenovirus Type 2 and the ts4 mutant which accumulates such particles were analysed by agarose gel electrophoresis, restriction endonuclease cleavage and blot hybridization techniques. IP DNA consisted of a heterogeneous population of subgenomic-size DNA (IPSD1) and smaller molecules ranging from about 1,000 base pairs to 200 base pairs (IPSD2). IPSD1 from ts4 was more heterogeneous than that from wild-type, but both contained sequences from all parts of the viral genome. IPSD2 contained heterogeneous cellular sequences and viral sequences from the left 4.4% of the genome. An endonuclease activity associated with IP and virions was capable of digesting viral or cellular DNA to IPSD2-like fragments suggesting a possible origin for these molecules. (Author abstract) (41 Refs)

27. THE DISTRIBUTION OF GUANINE - CYTOSINE PAIRS IN ADENOVIRUS DNAS.

Tikchonenko TI, Dubichev AG, Lyubchenko YuL, Kritko NP, Chaplygina NM, Kalinina TI, Dreizin RS, Naroditsky BS
D. I. Ivanovsky Inst. Virology, U.S.S.R. Acad. Medical Sciences, Moscow, USSR
J Gen Virol; 54(part2):425-429 1981

The distribution of guanine-cytosine (GC) pairs in the DNA of the highly oncogenic simian adenovirus Type 7 (SA7) and the non-oncogenic human adenovirus Type 6 (Ad6) has been studied by thermal denaturation and CsCl density-gradient centrifugation. The differential of the DNA thermal denaturation curves shows the presence of pronounced peaks which indicates uneven distribution of GC pairs along the DNA chains and the presence of regions with GC content from 30 to 74% in SA7 DNA and from 40 to 68% in Ad6 DNA. The DNA restriction fragments obtained by treatment with EcoRI, BamHI, SalI, BglII and HindIII were subjected to CsCl density-gradient centrifugation. GC content of the fragments ranged from 45 to 70% for SA7 DNA and from 43 to 61% for Ad6 DNA. The GC content of the extreme left-hand fragments, where the transforming gene(s) is located, was higher than the av for SA7 DNA and lower than the av for Ad6 DNA. The most GC-rich regions were localized in the center of the genome. The GC content of the right-hand part of both viral genomes was lower than the av. (Author abstract) (17 Refs)

28. ONCOGENICITY OF GIBBON RETROVIRUS DETERMINED BY LEUKEMIA-SPECIFIC GENOMIC SEQUENCES.

Sun L, Kawakami TG
(c/o Kawakami) Comparative Oncology Lab., Univ. California, Davis, CA, 95616
Virology; 114(1):261-264 1981

The genome of a Type C virus, GaLV-5, isolated from several clinically healthy gibbons, was examined for the presence of nucleotide sequences related to the myelogenous leukemia-specific 'MYE' RNA and the lymphocytic leukemia-specific 'LYM' RNA which have been isolated from several strains of oncogenic GaLV. The genomes of these oncogenic GaLVs were each separated into sequences homologous and nonhomologous to GaLV-5. Based on hybridization analysis, the nonhomologous RNA fractions were found to contain either the

MYE RNA or the LYM RNA. This indicates that the leukemia-specific RNAs are lacking in the genome of GaLV-5. This lack was further confirmed by analysis of hybridization kinetics. The presence of leukemia-specific RNA sequences in GaLV genomes that were isolated from animals with leukemia and the absence of these sequences in virus strains isolated from animals free of clinical symptoms of leukemia indicate that the leukemia-specific RNA sequences are closely associated with the oncogenesis of leukemia in gibbons. (Author abstract) (17 Refs)

29. NUCLEIC ACID HOMOLOGY BETWEEN AVIAN AND MAMMALIAN TYPE C VIRUSES: RELATEDNESS OF RETICULOENDOTHELIOSIS VIRUS CDNA TO CLONED PROVIRAL DNA OF THE ENDOGENOUS COLOBUS VIRUS CPC-1.

Rice NR, Bonner TI, Gilden RV
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Virology; 114(1):286-290 1981

Reverse transcriptase and p30 of the reticuloendotheliosis viruses (REV), which are Type C viruses horizontally transmitted among certain avian species, have previously been shown to be related to mammalian rather than to other avian leukosis/sarcoma Type C viral proteins. Though the closest homology has been seen between proteins of REV and those of the endogenous macaque viruses (MAC-1 and MMC-1), relatedness of their nucleic acids cannot be detected by routine liquid hybridization. We report here that nucleic acid homology between REV and the colobus monkey endogenous virus (CPC-1), which is highly related to the macaque viruses, can be demonstrated when hybridization is carried out with highly labeled [32P]cDNA and cloned viral DNA immobilized on nitrocellulose. Related regions occur within both the pol and the gag genes of the colobus viral genome. Thus, the REV family of viruses appears to be descended from an ancestral virus which also gave rise to the MAC-1, MMC-1, CPC-1 group of viruses now endogenous in primates. (Author abstract) (20 Refs)

30. DETECTION AND CLONING OF MURINE LEUKEMIA VIRUS-RELATED SEQUENCES FROM AFRICAN GREEN MONKEY LIVER DNA.

Martin MA, Bryan T, McCutchan TF, Chan HW
Lab. Molecular Microbiology, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
J Virol; 39(3):835-844 1981

By using low-stringency nucleic acid hybridization conditions and specific subgenomic segments of the AKR ecotropic provirus as probes, murine leukemia virus (MuLV)-related sequences wer e detected in African green monkey (AGM) liver DNA. The MuLV-reactive segments present in restricted AGM DNA ranged from 1.9 kilobases (kb) to greater than 10 kb in size. On the basis of this finding, a 17-kb segment was cloned from a partial EcoRI AGM library in lambda Charon 4A which shared nearly 5 kb of homology with AKR ecotropic MuLV DNA. The MuLV-related sequences detected in restricted preparations of AGM DNA or present in the cloned monkey DNA reacted with probes mapping 2.0 to 7.0 kb from the 5' terminus of the AKR ecotropic provirus. The AGM clone also contained repeated sequences that flanked the MuLV-related segment. Labeled, subgenomic, MuLV-reactive segments of the monkey clone hybridized to multiple restriction fragments of AGM liver DNA, indicating the presence of several copies of the MuLV-related sequences. (Author abstract) (48 Refs)

IMMUNOLOGICAL STUDIES

31. EPSTEIN-BARR VIRUS STRAIN- AND GROUP-SPECIFIC ANTIGENIC DETERMINANTS DETECTED BY MONOCLONAL ANTIBODIES.

Mueller-Lantzsch N, Georg-Fries B, Herbst H, Zur Hausen H, Braun DG
Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Int J Cancer; 28(3):321-327 1981

In order to differentiate Epstein-Barr virus (EBV) strains by serological markers we prepared hybridomas producing monoclonal antibodies against polypeptides of the QIMR-WIL EBV strain. These monoclonal antibodies were screened by indirect immunofluorescence techniques. Immunoprecipitation, using EBV-positive monoclonal antibodies and the protein A method, of 125I-labeled polypeptides from purified QIMR-WIL EBV particles, revealed that a series of monoclonal antibodies against the four main surface and envelope polypeptides precipitating p340, p340/p240, p140, and p80 were obtained. When 125I-labeled polypeptides from purified P3HR-1 and B95-8 EBV particles were immunoprecipitated, it could be demonstrated that several anti-p340 (QIMR-WIL) antibodies recognized strain-specific antigenic determinants, while anti-p340/p240 (QIMR-WIL) as well as anti-p140 (QIMR-WIL) antibody clones reacted with antigenic sites which are in common wither among B95-8 or in addition to P3HR-1 polypeptides, Thus, monoclonal antibodies now provide a serological basis for EBV typing. (Author abstract) (31 Refs)

32. ANALYSIS OF THE NONVIRAL ANTIGENS IMMUNOPRECIPITABLE BY SV40 T ANTIBODY FROM SV40-TRANSFORMED HUMAN/MOUSE HYBRID CELL LINES.

Stitt DT, Mangel WF
(c/o Mangel) Dept. Biochemistry, Univ. Illinois, Urbana, IL, 61801
Virology; 114(1):149-160 1981

The expression of nonviral antigens, ie, host-coded proteins with mol wt from 48,000-56,000 (48K-56K) immunoprecipitable from extracts of simian virus 40 (SV40)-infected or -transformed cells by anti-SV40 tumor antibody, was examined in four SV40-transformed human cell lines, one SV40-trans formed mouse cell line, and eight SV40-transformed human/mouse somatic cell hybrid cell lines produced by fusion of SV40-transformed human cells with untransformed mouse cells. Differences were found in the patterns of expression of these viral induced proteins among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. Two of the human cell lines expressed only a 55K nonviral antigen; two expressed both a 55K and a 52K nonviral antigen. The mouse cell line expressed both a 55K and a 48K nonviral antigen. Each hybrid cell line expressed a 55K and also a 48K nonviral antigen, except one. The BALB IV-8 hybrid cell line expressed 55K and 52K nonviral antigens. By comparing the tryptic peptides fractionated on cation exchange columns of the nonviral antigens we determined: (1) the 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the BALB IV-8 human/mouse hybrid is encoded by a mouse chromosome. It is possibly a precursor to the mouse 48K protein because it contains one extra tryptic peptide in addition to those of the mouse 48K protein, because one peptide has an altered mobility and because the 52K protein is found, so far, only in a human/mouse hybrid that does not exhibit a 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybrid is encoded by a human chromosome. In the BALB IV-8 human/mouse hybrid, there is a 55K protein encoded by a human chromosome and probably a 55K protein encoded by a mouse chromosome. (4) If the gene encoding the human 55K nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (Author abstract) (25 Refs)

33. NATURAL ANTIBODIES TO THE HUMAN T CELL LYMPHOMA VIRUS IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA.

Posner LE, Robert-Guroff M, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Fossieck B, Bunn PA, Minna JD, Gallo RC
Lab. Tumor Cell Biology, NIH, Bethesda, MD, 20205
J Exp Med; 154(2):333-346 1981

Serum samples were obtained from patients with cutaneous T cell lymphoma (CTCL) and leukemia, and from 55 normal random donors. Retroviruses HTLV-CR (grown in HUT 102 cells) and HTLV-MB, isolated from patients CR and MB, respectively, were used, along with several other retroviruses. The sera were screened for the presence of natural antibody to HTLV-CR, using a solid-phase radioimmunoassay. Sera from patient CR and one other patient reacted specifically with proteins of HTLV-CR. CR serum also reacted with HTLV-MB proteins. Solid-phase immunocompetition and competition radioimmunoprecipitation assays demonstrated the specificity for HTLV-CR proteins. Patient CR antibodies were directed against viral core proteins with mol wt of 24,000 and 19,000, as shown by radioimmunoprecipitation analysis. Some reactivities to other animal retroviruses, including the baboon endogenous virus, simian sarcoma virus, feline leukemia virus, and gibbon ape leukemia virus, were demonstrated. These reactivities apparently were not virus-specific, but related to cellular antigen contamination of viral preparations or to antigens in fetal calf serum. The results indicate for the first time a specific antibody reaction to a retrovirus in humans. (38 Refs)

34. REACTIVITY OF ANTISERA TO ANTIGENS OF C-TYPE VIRUSES WITH LEUCOCYTES FROM PATIENTS WITH ACUTE LEUKAEMIA.

Pullen S, Hersey P
(c/o Hersey) Kanematsu Memorial Inst., Sydney Hosp., Macquarie St., Sydney, Australia 2000
Pathology; 13(2):289-298 1981

A number of previous studies have suggested that certain C-type viruses from non-human primates are associated with acute leukemia in humans. The present study sought to examine this association further by detection of antigens related to these viruses on the surface of acute leukemia cells. Antisera against the whole viruses or the major internal protein of simian sarcoma, endogenous baboon and Rauscher viruses were tested against mononuclear cells from patients with acute leukemia at various stages of their disease in 51Cr release WBC dependent cytotoxic assays. A high proportion of the patients had antigens related to these viruses detectable on their blood WBC at some stage in their disease whereas with one exception blood WBC from non-leukemic subjects did not. The expression of these antigens did not show a close relation to the number of blast cells in blood detected on morphological grounds. Antigens related to the non-human primate viruses were detected on mononuclear cells from bone marrow samples of several non-leukemic patients which indicated they were not specifically associated with leukemia. Antigens related to the Rauscher virus were detected on cells of practically all bone marrow samples tested. These results suggest that assays to detect these antigens would be of limited usefulness to monitor disease activity in patients with acute leukemia. Their expression on blood WBC however appeared strongly associated with acute leukemia and further studies to assess the prognostic and epidemiological significance of detection of these antigens appears warranted. (Author abstract) (16 Refs)

35. POSSIBLE ASSOCIATION BETWEEN ONCOGENIC VIRUSES AND HUMAN BREAST TUMORS.

Il'in KV, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):10-18 1981

Literature data on the association between human breast tumors and at least two oncogenic viruses are reviewed. Immunodiffusion with autoradiography showed the presence of protein with antigenic determinant similar to that of antigen p27 in 11/23 breast fibroadenoma specimens. The speci mens of malignant breast tumors did not contain the antigenic determinant of simian virus type D. The specimens of human breast carcinoma were found to contain the antigen similar to the major envelope protein gp52 of murine virus of mammary gland. The presence of gp52 antigen was not correlated either with the age of the patient or with the histology of the tumor. (48 Refs) (In RUS)

VIRAL STUDIES IN HUMAN CANCER

36. BURKITT'S LYMPHOMA.

Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

Recent developments that have added to the understanding of biologic, etiologic, and clinical aspects of Burkitt's lymphoma (BL) are reviewed. Detailed discussions present the immunology of malignant lymphoma, and etiology, clinical features, staging, treatment, and immunology of BL. BL now ranks with the dozen neoplasms that can be cured by drugs alone. BL is also the leading candidate for a virus-induced human tumor; studies of this association led to the discovery of Epstein-Barr virus as the cause of infectious mononucleosis. Experimental and clinical examination of BL have greatly expanded the study of immunobiology and tumor immunology. (121 Refs)

37. ASSOCIATION OF EPSTEIN-BARR VIRUS WITH NASOPHARYNGEAL CARCINOMA IN ALASKAN NATIVE PATIENTS: SERUM ANTIBODIES AND TISSUE EBNA AND DNA.

Lanier AP, Bornkamm GW, Henle W, Henle G, Bender TR, Talbot ML, Dohan PH
Alaska Investigation Div., Centers for Disease Control, 225 Eagle St., Anchorage, AK, 99501
Int J Cancer; 28(3):301-305 1981

Biopsy specimens from Alaskan Native patients with nasopharyngeal carcinoma (NPC) and from other patients seen on the otolaryngology service were tested for Epstein-Barr virus-specific DNA and nuclear antigen (EBNA). Serum samples from both groups were tested for various EBV-related antibodies. EBV DNA and EBNA results were in agreement in 29 of 31 tissue specimens tested by the two methods. Ten of 11 biopsies containing NPC cells were positive for EBV DNA. Two NPC patients had biopsies that showed only atypical epithelium but were also positive for EBV DNA or EBNA. The other tissue specimens were negative except for biopsies from two patients: one with a parotid gland lymphoepithelial lesion; another with undifferentiated carcinoma of salivary gland origin. (Author abstract) (28 Refs)

38. INFECTION WITH EPSTEIN-BARR VIRUS AND TUMOR ORIGIN IN THE HUMAN.

Kirchner H
Deutsches Krebsforschungszentrum, Institut fur Virusforschung, D-6900 Heidelberg, W. Germany
Naturwissenschaften; 68(8):418-422 1981

The Epstein-Barr Virus (EBV) is the only infectious agent for which a close association with human malignant tumors has been clearly demonstrated. These tumors are one type of nasopharyngeal carcinoma which is frequent in parts of East Asia and the Burkitt lymphoma which predominantly occurs in parts of Africa and New Guinea. Nonetheless, the EBV is the causative agent of infectious mononucleosis (IM), a benign, self-limiting lymphoproliferative disease of adolescents. The major difference between the countries in which the EBV-induced tumors occur and those in which IM occurs is the late primary EBV infection in the latter, whereas primary infection with EBV occurs in the first yr of life in the former. All theories of viral carcinogenesis have to explain the long latency period between primary infection and tumor growth and how an ubiquitous virus may be oncogenic. Thus, invariably, one has to assume a role of cofactors, which may be of cytogenetic nature or may be represented by additional infections or by chemical agents. Since most modern theories of carcinogenesis consider a multi-step development of tumors, the theory that infection with an ubiquitous virus at the right time of life represents one step to carcinogenesis seems to be tenable. (Author abstract) (7 Refs) (In GER)

39. BURKITT'S LYMPHOMA IN JAPAN: CLINICOPATHOLOGICAL FEATURES OF TWENTY-TWO PATIENTS.

Abe K, Sato T
Dept. Pediatrics, Hokkaido Univ. Sch. Medicine, Kitaku, Sapporo 060, Japan
Tohoku J Exp Med; 134(3):289-293 1981

Twenty-two cases of Burkitt's lymphoma in Japan were reviewed and their clinicopathological features were compared with those reported in African and American patients. There were 14 males, 8 females; aged 1-29 yr, mean age 9.5 yr. Most (19) were between 1 and 15 yr old. Five were Stage I, eight Stage II, six Stage III, and three Stage IV. Sites of involvement included the facial bone (20), abdomen (8), exophthalmus (5), cranial neuropathy (3), paraplegia (1), testes (1), and breast (1). The bone marrow was involved and leukemic transformation was observed in seven patients during the course of their disease. One of 17 patients tested for antibody titers to Epstein-Barr virus had a significantly elevated level. Serum lactic dehydrogenase levels were lower in patients with localized disease than those with advanced disease. The mean survival was 3.8 mo after diagnosis and no significant differences were found between the stage of disease and survival. (16 Refs)

40. GENITAL HERPES SIMPLEX.

Tummon IS, Dudley DK, Walters JH
214 Keyworth Ave., Ottawa, Ontario K1Y 0E9, Canada
Can Med Assoc J; 125(1):23-29 1981

Genital herpes is a sexually transmitted disease caused by the herpes simplex virus. Following the initial infection the virus becomes latent in the sacral ganglia. Approx 80% of patients are then subject to milder but unpredictable recurrences and may shed the virus even when they are asymptomatic. The disorder causes concern because genital herpes in the mother can result in rare but catastrophic neonatal infection and because of a possible association between genital herpes and cancer of the cervix. No effective treatment is as yet available. Weekly monitoring for virus by cervical culture from wk 32 of gestation is recommended for women with a history of genital herpes and for those whose sexual partner has such a history. (Author abstract) (70 Refs)

NATURAL HISTORY OF CERVICAL DYSPLASIA.

Spriggs AI
Lab. Clinical Cytology, The Churchill Hosp., Headington, Oxford OX3 7LJ, England
Clin Obstet Gynaecol; 8(1):65-79 1981

Incidence, pathogenesis, etiology, and treatment of cervical dysplasia are reviewed. Occurrence of dysplasia in previously unscreened women ranged from 0.5% to 6.5% (in different studies). The highest incidence of dysplasia was recorded in a 20-29 yr age group, while carcinoma in situ was predominant in a 30-39 yr age group. Follow-up studies of the patients with cervical dysplasia showed progression to invasion in 0.8-21% of the patients. Etiology of cervical dysplasia may be associated with Herpes simplex virus or with condyloma virus. Cytogenetic studies showed the hyperploidy and variation in DNA content. Evidence of aneuploidy was found even in the mild dysplasias. Conservative management of dysplasia (colposcopy followed by local destruction) is currently the treatment of choice. (66 Refs)

42. SEROEPIDEMIOLOGICAL STUDY OF HERPESVIRUS TYPE 2 AND CARCINOMA OF THE CERVIX.

Ohwada N
Dept. Obstetrics and Gynecology, Sch. Medicine, Gunma Univ., Maebashi-shi, Guma Pref. 371, Japan
Kitakanto Igaku; 31(2):87-97 1981

Sera obtained from patients with preinvasive and invasive cervical cancer, and ovarian and corpus cancer as well as from healthy control women were tested for neutralizing antibodies to herpesvirus type 1 (HSV-1) and type 2 (HSV-2) in regard to a possible association between HSV-2 and cervical cancer. Antibody titers to each virus type were determined simultaneously by a microtiter technique. The percentage of women with cervical cancer who had anti-HSV-2 antibody was significantly higher than that of patients with corpus and ovarian cancer and control women; cervical cancer patients 81%, corpus and ovarian cancer patients 26%, and control women 20%. However, the percentage of women having anti-HSV-1 antibody in the study group was comparable to that in the control group; cervical cancer patients 37%, corpus and ovarian cancer patients 39%, and control women 28%. The mean titer of neutralizing activity to HSV-2, as given by log2 of the reciprocal of the final serum dilution that exhibited the neutralizing activity, in the cervical cancer group (2.41 +-1.22) was also significantly higher than that in the corpus and ovarian cancer group (0.87 +-0.89) and in the control women (0.83 +-

0.97). This difference was independent of age. It has been noticed that in some patients with cervical cancer, especially in the stage of carcinoma in situ, the neutralizing antibody titers decreased significantly after surgical resection o the cancer tissues. These findings suggest a strong association between HSV-2 infection and the establishment of cervical cancer, although it is not clear whether the virus has a causative role in the development of cervical cancer or not. (36 Refs) (In JPN)

43. HERPESVIRUS-INDUCED ANTIGENS IN SQUAMOUS-CELL CARCINOMA IN SITU OF THE VULVA.

Kaufman RH, Dreesman GR, Burek J, Korhonen MO, Matson DO, Melnick JL, Powell KL, Purifoy DJ, Courtney RJ, Adam E

Dept. Obstetrics and Gynecology, Baylor Coll. Medicine, Houston, TX, 77030

N Engl J Med; 305(9):483-488 1981

Tissue and serum specimens from 19 patients (24-79 yr old) with squamous-cell carcinoma (SCC) in situ of the vulva (10 patients), severe dysplasia (1), condyloma acuminatum (4), and controls seen for periodic check-up (4), were evaluated for herpes simplex virus Type 2 (HSV2) DNA-binding proteins. Nine of 10 biopsy specimens from patients with SCC or severe dysplasia reacted strongly when stained with anti-ICPS34/35 (rabbit antiserum to HSV2-infected-cell-specific protein 34/35), and eight also reacted with anti-VP143 (rabbit antiserum to nonstructural HSV2 protein); five also reacted with anti-ICSP11/12 (rabbit antiserum to HSV2-infected-cell-specific protein 11/12). All the positive reactivity observed with anti-ICSP34/35, anti-ICSP11/12 and anti-VP143 was localized in the cytoplasm rather than the nuclei, as has been previously reported in infected cells. Whole-virion structural antigens were not observed, although serological evidence of previous HSV2 infection was found in patients tested for the presence of antibodies. Serum antibodies to HSV2 were noted in nine patients with SCC, including one with mild dysplasia, and two with normal tissue. The parallel rise in the incidences of HSV2 infection and of vulvar SCC in situ and the demonstration of HSV2-specific proteins in this tissue suggest an association of HSV2 infection with this cancer. (17 Refs)

44. TYPE 2 HERPES SIMPLEX VIRUS AND VULVAR CARCINOMA IN SITU.

Schwartz PE, Naftolin F

Yale Univ. Sch. Medicine, New Haven, CT, 06510

N Engl J Med; 305(9):517-518 1981

The association between herpes simplex virus Type 2 (HSV2) infection and the development of vulvar squamous cell carcinoma in situ (CIS) is discussed. The incidences of HSV2 infection and CIS of the vulva have risen dramatically in recent yr. The malignant potential of vulvar CIS remains to be established. The question of whether HSV2 infection is etiologically involved in the malignant transformation of CIS cells or is merely an opportunistic infection must be answered. The oncogenic potential of HSV2 for vulvar neoplasms must be investigated. (9 Refs)

45. SEARCH FOR GENETICAL INFORMATION OF HERPES SIMPLEX VIRUS IN CERVICAL TUMOR TISSUE BY METHOD OF TRANSFECTION.

Kniazev PG, Vasiljev BV, Iovlev VI, Zhudina AI, Pluzhnikova GF, Chernina LA, Gaber VK, Dyad'kova AM, Bokhman YV, Smorodintsev AA, Seitz IF

N. N. Petrov Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR

Vopr Onkol; 27(7):51-56 1981

Virus-specific information (DNA of herpes virus) is obtained by the method of transfection in purified preparations of the DNA from cervical tumor tissue cells, negative to whole viral particles of herpes simplex Type 2. No evidence pointing to DNA preparations free from infectious forms of the genome of herepes virus, being capable of transforming human embryonal cells is found. (Author abstract) (5 Refs) (In RUS)

46. IMMUNOPEROXIDASE LOCALIZATION OF PAPILLOMAVIRUS ANTIGENS IN CERVICAL DYSPLASIA AND VULVAR CONDYLOMAS.

Kurman RJ, Shah KH, Lancaster WD, Jenson AB

Dept. Obstetrics and Gynecology, Georgetown Univ. Hosp., 3800 Reservoir Road, Washington, DC, 20007

Am J Obstet Gynecol; 140(8):931-935 1981

Biopsies of 50 cases of cervical dysplasia (46 mild and 4 moderate) and 40 cases of vulvar condyloma acuminata (genital warts) were screened for the presence of papillomavirus antigens by means of a peroxidase-antiperoxidase method having immunospecificity against the genus-specific (common) antigen(s) of the papillomaviruses. With the use of this technique, on formalin-fixed, paraffin-embedded tissue, papillomavirus antigens were detected in cells with cytologic and histologic features of wart virus infection (so-called koilocytotic atypia). Cells showing a positive reaction for papillomavirus antigens were identified in 24 of 50 (48%) cases of cervical dysplasia and 20 of 40 (50%) cases of vulvar condyloma. The results of this study provide specific confirmation of the presence of papillomavirus antigens in cervical dysplasia and suggest that the papillomavirus may be an important factor in the etiology of this disease. (Author abstract) (18 Refs)

47. PAPILLOMAVIRUS AND CUTANEOUS MALIGNANCY.

Bender ME, Pass F

Dept. Dermatology, University Hospitals, Box 98, 420 Delaware St. S.E., Minneapolis, MN, 55455

Int J Dermatol; 20(7):468-474 1981

The relationship between papillomaviruses and malignancy in both the human and animal systems is reviewed. The structure, classification, and host-specificity of human papillomavirus (HPV) and the development and transmission of HPV-related warts are reviewed. The oncogenic conversion of papillomavirus-induced animal tumors, as studied in the rabbit and bovine systems, is reviewed. The Shope papilloma, a virus-induced epidermal neoplasm which is indigenous to western cottontail rabbits in the Mississippi River Valley, is discussed. The incidence of malignant degeneration of Shope papillomas is considered. In addition to the oncogenic potential of the virus alone, other factors including host genetic com position and extrinsic chemicals seem to be a factor in malignant conversion. The relationship between HPV and epidermoid carcinoma is discussed. Abnormalities, including epidermodysplasia verruciformis, laryngeal carcinoma developing from multifocal juvenile laryngeal papillomas, bowenoid papulosis, genital carcinoma in situ, and verrucous carcinomas, are discussed in relation to HPV. (88 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

48. MECHANISM OF INHIBITION OF EPSTEIN-BARR VIRUS REPLICATION BY PHOSPHONOFORMIC ACID.

Datta AK, Hood RE
Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Virology; 114(1):52-59 1981

The trisodium salt of phosphonoformic acid (PFA) inhibits Epstein-Barr virus (EBV) replication in lymphoblastoid cells at concentrations nontoxic to cellular growth. The synthesis of early antigen (EA) in the infected cells is not affected by the drug under conditions when viral capsid antigen (VCA) and viral DNA synthesis are inhibited to the extent of 75 and 90%, respectively. In vitro studies with partially purified DNA polymerases show that PFA inhibits EBV-associated DNA polymerase to a greater extent than it inhibits alpha- and beta-polymerases. Enzyme kinetic analysis reveals a linear noncompetitive inhibition with four deoxytriphosphates and a typical uncompetitive inhibition with variable concentrations of DNA as substrate at saturating deoxytriphosphate concentrations. The apparent inhibition constant for EBV-associated polymerase was in the range of 2-3 uM. The inhibitory effect is exerted at the pyrophosphate binding site of DNA polymerase. Although productive viral DNA synthesis is completely arrested by the drug, the virus-associated DNA polymerase activity is expressed normally in superinfected Raji cells even in the presence of the drug. We propose that in addition to potential therapeutic value, the compound could be used as a tool to study some of the restricted early functions of virus in the absence of productive viral DNA synthesis. Induction of viral DNA polymerase can also be used as an additional marker for expression of early viral functions. (Author abstract) (36 Refs)

49. USAGES OF INTERFERON AND INTERFERON INDUCERS IN MAN: THE SECOND HALF OF 1980.

Pollard RB
Dept. Medicine, Univ. Texas Medical Branch, Div. Infectious Diseases, Galveston, TX
Med Biol; 59(2):69-76 1981

Utilizing the systematic nomenclature for interferons used in research and clinical trials, some aspects of human leukocyte interferon (HuIFN-alpha) and human fibroblast interferon (HuIFN-beta) are reviewed. HuIFN-alpha is discussed with respect to its effects on herpes simplex virus and Epstein-Barr virus infections, its effects on hepatitis B virus and other virus infections in patients treated for other disorders, its effects in malignancy, its cellular effects, and its effects in miscellaneous disorders (Creutzfeldt-Jacob disease, schizophrenia, and psychotic depression). HuIFN-beta is reviewed with respect to its effects on various virus infections (such as rhinovirus and adenovirus infections) and the cutaneous reactions and side effects that are observed in its use. The association of keratopathy, significant retinal mottling, and arteriolar narrowing (related to decrease in visual field size) with the administration of the interferon inducer tilorone is documented. Implications of some of the reported findings are discussed. (22 Refs)

50. IMMUNOPOTENTIATION AND INHIBITION OF HERPES VIRUS ACTIVATION DURING THERAPY WITH LITHIUM CARBONATE.

Lieb J
41 Village Lane, Bethany, CT, 06525
Med Hypotheses; 7(7):885-890 1981

The successful treatment of nine patients (5 women, 4 men; aged 18-44 yr) with recurrent respiratory tract infections and other recurrent manifestations of defective immunity with lithium carbonate is reported. In addition, four patients (3 women, 1 man; aged 20-58) with recurrent herpes labialis treated with lithium also went into remission; in two patients, the effect appeared to be dose-dependent. (23 Refs)

GENERAL REVIEWS

51. CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY OF GYNECOLOGIC TUMORS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Clinical Immunology and Immunotherapy of Gynecologic Tumors (Cancer Overview) Freedman, R S, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922802:; OT-81/02:52pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Overview includes all clinical aspects of the immunology and immunotherapy of gynecologic tumors. Immunologic studies of gestational trophoblastic disease include paternal antigen expression, human leukocyte antigen histocompatibility, and immunoassays of betaglycoprotein and human chorionic gonadotropin (HCG). Antigenic studies of the uterine cervix include herpes viruses, cytomegaloviruses, tumor-associated antigens, carcinoembryonic antigens and beta oncofetal antigens. Studies of cellular immune response, lymph node morphology and lymphocytic infiltration as prognostic indicators of the uterine cervix are covered as well as the effects of radiotherapy on the immune status of patients with cervical carcinoma. Immunologic aspects of ovarian tumors which are covered include human ovarian tumor-associated antigens and oncofetal antigens. Non-specific, active specific, and other immunotherapeutic trials in gynecologic neoplasms are also included in this Overview.

52. FUNCTIONS OF T ANTIGENS OF SV40 AND POLYOMAVIRUS.

Hand R
McGill Cancer Centre, McGill Univ., 3655 Drummond, Montreal, Quebec, H3G 1Y6, Canada
Biochim Biophys Acta; 651(1):1-24 1981

Functions of the tumor or T antigens of SV40 and polyomavirus are reviewed. Topics discussed include genome organization (SV40 genome, polyomavirus genome, and comparison of maps), proteins of the early regions (SV40 antigens, polyomavirus T antigens, and super T antigens), functions of T antigens (small t antigen, middle T antigen, and large T antigen), other immunoreactive T antigens (tumor-specific transplantation antigens, U antigen, and cellular proteins bound by antibodies against SV40 T antigens), large T antigen binding to DNA, viral DNA synthesis, cellular DNA synthesis (SV40 and polyomavirus), adenovirus helper function, regulation of viral transcription, integration of viral DNA, enzyme reactivities associated with T antigens (SV40 and polyomavirus), T antigens and transformation (SV40, polyomavirus, and A and N transformants), and conclusions. (196 Refs)

53. WARTS: A CLINICIAN'S VIEW.

Rees RB
Dept. Dermatology, Univ. California Sch. Medicine, San Francisco, CA
Cutis; 28(2):175-178,180 1981

A review of research and clinical treatment pertaining to the human papilloma virus (HPV) is provided. Topics discussed include detecting wart viruses in human papillomas, the number of wart viruses known to exist, whether a wart vaccine is possible, studies on epidermodysplasia verruciformis, culturing the human wart virus, vaginal condylomata in the mother with laryngeal form in the child, difficulty in demonstrating the wart virus, whether warts regress through an immune mechanism, whether HPVs are oncogenic, and the various treatments in practice. (28 Refs)

54. TUMOR VIRUSES OF NONHUMAN PRIMATES.

Wunderlich V, Micheel B
Zentralinstitut fur Krebsforschung der AdW der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(3):242-261 1981

Tumor viruses have been isolated in increasing numbers from nonhuman primates in recent yr. Currently-known viruses are reviewed. Among the DNA viruses, the papovaviruses have been isolated only from Old World monkeys. Adenoviruses have been found in Old and New World monkeys and apes. Alpha-herpesviruses have not been shown to be related to neoplasms. Beta-herpesviruses have been shown to be related to such human viruses as the Epstein-Barr virus. Also discussed are pox viruses and hepatitis B. Among the RNA viruses are several families not considered relevant to tumor research. Among those considered relevant are the Type C and Type D retroviruses. Experimental evidence of the relationships among nonhuman primate viruses and with human viruses is useful in determining the etiology of human viruses. (134 Refs) (In GER)

OTHER RELATED STUDIES

55. THE DETECTION OF EPSTEIN-BARR VIRUS RECEPTORS UTILIZING RADIOLABELLED VIRUS.

Koide N, Wells A, Volsky DJ, Shapiro IM, Klein G
Dept. Internal Medicine, Okayama Univ. Sch. Medicine, 5-1, 2-chome, Okayama 700, Japan
J Gen Virol; 54(part1):191-195 1981

Epstein-Barr virus (EBV) was labeled with 3H-thymidine and purified about 1000-fold from the culture medium by ultracentrifugation on 5 to 30% dextran gradients. The presence of the virus was monitored by radioactivity and Epstein-Barr virus-determined nuclear antigen (EBNA) induction in sensitive indicator cells (Ramos). Peaks for both activities occurred in the 17 to 18% dextran fractions. Unlabeled virus recovered in the peak fraction was labeled with 125I. Both thymidine and 125I-labeled purified virus bound quantitatively to receptor-positive Burkitt lymphoma-derived cell lines but not to EBV-receptor-negative T-lymphocyte-derived cell lines. Thymidine-labeled virus that was allowed to bind to Raji cells was present in the interior of briefly trypsinized cells after 3 hr incubation at 37 C. The results provide a convenient method for detecting the EBV receptor by radioactively labeled virus. (Author abstract) (15 Refs)

56. INDUCTION OF COMPLEMENT RECEPTOR EXPRESSION IN CELL LINES DERIVED FROM HUMAN UNDIFFERENTIATED LYMPHOMAS. II. CHARACTERIZATION OF THE INDUCED COMPLEMENT RECEPTORS AND DEMONSTRATION OF THE SIMULTANEOUS INDUCTION OF EBV RECEPTOR.

Magrath I, Freeman C, Santaella M, Gadek J, Frank M, Spiegel R, Novikovs L
Pediatric Oncology Branch, NCI, Bethesda, MD, 20205
J Immunol; 127(3):1039-1043 1981

We have studied the specificity of complement receptors induced by theophylline in two cell lines derived from undifferentiated lymphomas, one of Burkitt's type, and compared it to that of complement receptors in other cell types. Both C3b and C3d receptors were induced. The induced C3b receptor differed from the C3b receptor of mature normal lymphocytes, polymorphonuclear leukocytes and the cells of a nodular lymphoma in two respects. Firstly, it bound C3b much less avidly (by a factor of several hundred-fold) and secondly, we were unable to demonstrate C4b binding. EBV receptors were induced at the same time as complement receptors, and permitted the conversion of a greater fraction of cells to EBNA positivity after experimental infection with EBV. The induction of receptors was not associated with a change in the fluidity of the plasma membranes and our data do not favor a different orientation of induced receptors within the membrane as compared to receptors of other cell types - a potential explanation for the different specificities. Our findings are consistent with the possibility that the complement receptors of lymphocyte precursors differ from those of mature lymphocytes. (Author abstract) (20 Refs)

57. LYMPHOBLASTOID CELL LINES, TRANSFORMED BY EPSTEIN-BARR VIRUS, IN THE ENZYMATIC STUDY OF HEREDITARY LYSOSOMAL STORAGE DISEASES.

Watanabe Y, Minami R
Dept. Pediatrics, Sapporo Medical Coll., Sapporo 060, Japan
Tohoku J Exp Med; 134(3):229-243 1981

The levels of eight lysosomal enzymes were measured in Epstein-Barr virus-transformed lymphoblastoid cells from 11 patients with hereditary lysosomal storage diseases, including two cases of GMI-gangliosidosis, one of variant beta-galactosidase deficiency, one of Tay-Sachs disease, two of Gaucher disease, three of I-cell disease, one of Hurler syndrome, and one of Scheie syndrome. Twenty of the patients' heterozygotes and 20 control subjects were also studied. With the exception of I-cell disease, none of the enzymes that were deficient in the respective diseases were measured in the lymphoblastoid cells of that patient. Some low levels of enzyme activity were detected in cells from I-cell disease. Activity of beta-D-galactosidase from heterozygotes of the patient with GMI-gangliosidosis and alpha-L-iduronidase activity from heterozygotes of the patient with Hurler's syndrome were in the carrier range. In controls, two peaks on sephadex G-150 gel filtration were seen for beta-

D-galactosidase, while in patients with GMI-gangliosidosis, the first peak was markedly diminished and the second peak was absent; in heterozygotes, peak II was smaller than that of controls. In controls, both hexosaminidase A and hexosaminidase B were detected, while enzyme B was not detected in Tay-Sachs disease, and the ratios of enzyme A/B in the parents were lower than in controls. (22 Refs)

58. ENHANCED REACTIVATION OF ULTRAVIOLET-DAMAGED HERPES VIRUS IN ULTRAVIOLET PRETREATED SKIN FIBROBLASTS OF CANCER PRONE DONORS.

Coppey J, Menezes S
Institut Curie, Section de Biologie, 26 rue d'Ulm, 75231 Paris Cedex 05, France
Carcinogenesis; 2(8):787-793 1981

The enhanced reactivation (ER) of UV-damaged nuclear replicating DNA viruses was studied in host cells treated with UV prior to infection. Host cells were from normal (N), xeroderma pigmentosum (XP), excision proficient XP (XP variant), xerodermoid (XD), XP heterozygote (XH), epidermodysplasia verruciformis (EV), and miscellaneous donors. Cells received 260 nanom UV radiation (0.1-25 Joules/square meter [m2]) 0-60 hr before infection with intact (HSV) or UV-irradiated herpes simplex virus (UV-HSV). ER was max for all cell lines when the interval between irradiation of the host cells and infection with virus was 36 hr. In N, XH, XD, XP variant, EV Mibelli's porokeratosis, diffused nevomatosis, and Down's syndrome cell lines, ER was max at a UV dose of 15 Joules/m2. In XD, EV, and XP variant cells the ER was increased 10-fo ld over the ER in N cells. Max ER was obtained in three groups of XP cells with UV doses of 0.1, 0.3, and 2 Joules/m2. The results demonstrate that UV-HSV undergo ER when host cells are exposed to UV prior to infection. The ER is apparently brought about by an as yet undescribed transitory DNA repair mechanism in the host cells. (54 Refs)

59. INFECTION AND CANCER.

Alvarez Bermudez CA, Blanco Villalba JC, Trodler CR, Wul FL
Catedra de Oncologia, Facultad de Medicina. Universidad del Salvador, Av. Luis M. Campos 726, 7 piso 1426, Buenos Aires, Argentina
Prensa Med Argent; 68(4):139-143 1981

The infection is the most common and feared complication of cancer, especially in leukemias and lymphomas. The neutropenia produced by irradiation and chemotherapy is mostly responsible for the infection. Of the 150 patients with Hodgkin's and non Hodgkin's lymphomas, and myelomas, 76 were selected, because they completed the radiation therapy or at least chemotherapy. The time period was 1968-1980, 46 were men and 30 women, 40% were between 60-80 yr old. There were 36 Hodgkin's patients, 37 non Hodgkin's lymphomas and 3 myelomas. The 31 patients with infections had: bacterial (15), viral (12), tuberculosis (3), mycosis (1); 5 of them died (bacterial 3, tuberculosis 1, candidiasis 1). The most common locations were: lung, urinary tract, and skin. Of the viral infections 72.7% were due to Herpes zoster confirming its affinity to Hodgkin's disease. (23 Refs) (In SPA)

60. STUDIES ON THE INFECTIONS ACCOMPANYING CHEMOTHERAPY OF MALIGNANT LYMPHOMA (MEETING ABSTRACT).

Sando Y, Yasuoka M, Nishihara R, Ueoka H, Sato M, Hayashi K, Oka A, Nakata Y, Ohnoshi T, Kimura I
Second Dept. Internal Medicine, Okayama Univ., Medical Sch., Shikata-cho, Okayama 700, Japan
Nippon Monaikei Gakkai Kaishi; 21(1):99 1981

The incidence of infections in 57 patients with advanced-stage malignant lymphoma (13 Hodgkin's disease, 44 non-Hodgkin's disease) seen during the past 4 yr was compared with that of 66 patients with advanced lung cancer seen during about the same period. Both groups were given multichemical therapy, with cyclophosphamide as the principal drug, or combined therapy, with adriamycin as the principal drug, and prednisolone was used intermittently for only the patients with malignant lymphoma. The patients were considered to have infections when an infectious lesion was visible or when a temperature of 38 C or more continued for 3 days or more in progression. However, fevers due to unknown causes before therapy in the case of malignant lymphoma were excluded. During the hospitalization period 63% and 53% of the patients with malignant lymphoma and lung cancer, respectively, developed infections. The infection in the patients with malignant lymphoma was most frequently pneumonia (26%), and various other infections such as infections of t he urinary tract, herpes zoster, septicemia and varicella occurred. There were more viral infections in the patients with malignant lymphoma than in those with lung cancer. Of the patients with lung cancer, 66% had infections near the tumor, and only a few had pneumonitis in regions unrelated to the tumor, or herpes zoster. When the number of neutrophils decreased, a high incidence of infection was seen in both groups of patients compared to the period when there were more neutrophils. In particular, most of the lung cancer patients developed pneumonia when their neutrophil count was 1,000/mm3 or less while the patients with malignant lymphoma had pneumonia unrelated to the number of neutrophils. (no Refs) (In JPN)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. DIFFERENTIAL IMMUNOLOGIC REACTIVITY AND PROCESSING OF GLYCOPROTEINS GA AND GB OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 MADE IN VERO AND HEP-2 CELLS.

Pereira L, Dondero D, Norrild B, Roizman B
California Dept. Health Services, 2151 Berkeley Way, Berkeley, CA, 94704
Proc Natl Acad Sci USA; 78(8):5202-5206 1981

Herpes simplex virus Types 1 and 2 (HSV-1 and HSV-2, respectiely) specify five major glycoproteins designated as gA, gB, gC, gD, and gE. Previous studies have shown that gA and

HE 20. 3173/2:

gB differ in electrophoretic mobility but not in reactivity with antisera prepared to each of these glycoproteins. Moreover, gA and gB of HSV-1 crossreact in serologic tests with the corresponding glycoproteins of HSV-2. In this paper, we report on the reactivities of gA and gB of HSV-1 and HSV-2 with 24 independently derived monoclonal antibodies reactive with these antigens. Our results show the following: (i) Electrophoretic mobilities of HSV-1 and HSV-2 glycoproteins gA and gB made in HEp-2 cells are significantly less than those made in Vero cells. (ii) All monoclonal antibodies precipitated both gA and gB made in infected HEp-2 cells. These include 12 monoclonal antibodies that neutralized virus and 12 that did not. (iii) HSV-2 glycoproteins gA and gB made in HEp-2 cells contain type-specific domains. However, monoclonal antibodies produced by one clone directed to these domains did not react with glycoproteins made in Vero cells. (iv) Lysates of infected Vero cells contain three lower mol wt polypeptides that also reacted with monoclonal antibodies directed to glycoproteins gA and gB. These polypeptides are virus specific inasmuch as those specified by HSV-1 differ in electrophoretic mobilities from those specified by HSV-2. These polypeptides are absent in lysates of HEp-2 cells. (Author abstract) (21 Refs)

2. ANALYSIS OF THE DNA-TERMINAL PROTEIN FROM DIFFERENT SEROTYPES OF HUMAN ADENOVIRUS.

Rekosh D

Dept. Biochemistry, State Univ. New York at Buffalo, Buffalo, NY, 14214

J Virol; 40(1):329-333 1981

The DNA-terminal proteins from adenovirus Type 12, Type 3, and Type 5 were analyzed, after labeling in vitro with 125I by the chloramine T method, and were shown to be serotype specific. We also studied the kinetics of cleavage by alkali of the terminal protein-DNA linkage and showed that the half-time of cleavage with either 0.1 M NaOH or 0.5 M piperidine at 37 C is about 15 to 30 min. The substitution of the volatile base piperidine for NaOH in this procedure provided a useful tool for rapid analysis of the labeled protein. (Author abstract) (14 Refs)

3. ISOLATION OF A SV40-LIKE VIRUS FROM A PATIENT WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY.

Scherneck S, Geissler E, Janisch W, Rudolph M, Vogel F, Zimmermann W

Central Inst. Molecular Biology, DDR 1115, Berlin-Buch, E. Germany

Acta Virol (Praha); 25(4):191-198 1981

A SV40-like virus was isolated from the brain of a patient with progressive multifocal leukoencephalopathy. The virus was antigenically and serologically indistinguishable from SV40 wild type. A unique difference from SV40 was its ability to grow on human glial and CV-I monkey cells. The mol wt of the viral DNA was very similar to that of SV40 DNA and the DNA cleavage patterns obtained after digestion with Hind II and Hind III restriction endonucleases were indistinguishable from those of SV40. (Author abstract) (30 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

4. SEQUENCE COMPLEXITY OF CIRCULAR EPSTEIN-BARR VIRUS DNA IN TRANSFORMED CELLS.

Griffin BE, Bjorck E, Bjursell G, Lindahl T

Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England

J Virol; 40(1):11-19 1981

A simplified procedure, based on several methods previously used to isolate circular DNA molecules from bacteria, was devised for the preparation of covalently closed circular viral DNA molecules from large quantities of lymphocytes transformed by Epstein-Barr virus. The protocol can be applied both to virus nonproducer lines and to lines containing cells activated to virus production. Sufficient amounts of highly purified viral DNA of intracellular origin were obtained from B95-8 and Raji cells to allow direct visual analysis of their sequence complexities after cleavage with EcoRI and separation of fragments by gel electrophoresis. No major differences in complexity were observed between circular DNA and linear virion DNA from B95-8 cells. The fragment patterns observed in this fashion agree well with those detected by conventional blotting and hybridization methods. The procedure can also be used as an analytical method to assay for small amounts of circular Epstein-Barr virus DNA molecules in other transformed cells. In this connection, no circular Epstein-Barr virus DNA was detected in Namalva Cells. (Author abstract) (32 Refs)

5. PLEIOTROPIC EXPRESSION OF EPSTEIN-BARR VIRUS DNA IN HUMAN EPITHELIAL CELLS.

Stoerker J, Parris D, Yajima Y, Glaser R

(c/o Glaser) Dept. Medical Microbiology and Immunology, Coll. Medicine, Comprehensive Cancer Center, Ohio State Univ., Columbus, OH, 43210

Proc Natl Acad Sci USA; 78(9,part2):5852-5855 1981

We have attempted to establish a system that can be used to study the association of Epstein-Barr virus (EBV) with epithelial cells. Attempts were made to transfect human carcinoma cells with EBV DNA. Successful transfection was confirmed by the expression of EBV-specific early antigen (EA), virus capsid antigen, and the presence of virus DNA. The transfecting preparation contained a mixture of EBV and cellular DNA extracted from two producer cell lines, P3HR-1 and AG-876. Our data suggest that virus DNA obtained from the P3HR-1 nontransforming, EA-inducing strain of EBV was lytically expressed in the epithelial tumor cells. The DNA derived from AG-876 cells, which produce a transforming, non-EA-inducing strain of EBV, also produced a lytic infection. (Author abstract) (21 Refs)

6. CHROMOSOME 14 MARKERS IN TWO EPSTEIN-BARR VIRUS (EBV)-TRANSFORMED LYMPHOBLASTOID CELL LINES OF NORMAL ORIGIN DIFFER FROM THE BURKITT LYMPHOMA (BL)-ASSOCIATED 14Q+ MARKER.

Manolov G, Manolova Y, Klein G, Levan A, Kieler J

(c/o Klein) Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden

Cancer Genet Cytogenet; 4(2):179-184 1981

Two among 10 Epstein-Barr Virus (EBV)-transformed lymphoblastoid cell lines contained a 14q+ marker in a low frequency of the cells (2 and 9%). By means of 'mesome-prosome' analysis of the G-band patterns of these markers; it was established that the additional chromosome segments of these two 14q+ markers came from chromosomes 3 and 5, respectively, and not from chromosome 8 as in the 14q+ marker of Burkitt lymphoma. Chromosome 8 was not involved at all in any changes in the 10 lymphoblastoid cell lines studied. (Author abstract) (19 Refs)

7. INDUCTION OF URACIL-DNA GLYCOSYLASE AND DUTP NUCLEOTIDOHYDROLASE ACTIVITY IN HERPES SIMPLEX VIRUS-INFECTED HUMAN CELLS.

Caradonna SJ, Cheng Y
(c/o Cheng) Dept. Pharmacology and Medicine, Cancer Drug Development Program, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, 27514
J Biol Chem; 256(19):9834-9837 1981

HeLa BU cells infected with either the Type 1 or the Type 2 forms of herpes simplex virus show an increase in the activities of uracil-DNA glycosylase and dUTP nucleotidohydrolase. Under optimal conditions, uracil-DNA glycosylase activity increases approx 40-fold in HSV Type 2-infected cells. In herpes simplex virus (HSV) Type 1-infected cells, uracil-DNA glycosylase activity increases only 6-fold. At a KCl concentration of 100 mM, uracil-DNA glycosylase derived from HSV Type 2-infected cells is activated two-fold, while the glycosylase extracted from mock infected HeLa BU cells is inhibited almost 90% at 100 mM KCl. dUTP nucleotidohydrolase activity increases four-fold and three-fold, respectively, in HSV Type 1-and and HSV Type 2-infected HeLa BU cells. Nondenaturing polyacrylamide gel electrophoresis of extracts derived from the Type 1-and Type 2-infected cells indicates distinct electrophoretic mobilities from the host cell enzyme. dUTP nucleotidohydrolase RF values for the mock infected cells, HSV Type 1, and HSV Type 2 are 0.5, 0.25, and 0.33, respectively. Serum from rabbits immunized against cells infected with herpes simplex virus Type 1 or Type 2 specifically neutralizes the dUTPase and uracil-DNA glycosylase activities extracted from herpes simplex virus-infected cells. This serum does not neutralize dUTPase or uracil-DNA glycosylase activity derived from mock infected cells. (Author abstract) (26 Refs)

8. PHOSPHOLIPID SYNTHESIS IN HUMAN EMBRYO FIBROBLASTS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 2.

Daniel LW, Waite M, Kucera LS, King L, Edwards I
Dept. Biochemistry, Bowman Gray Sch. Medicine, Wake Forrest Univ., Winston-Salem, NC, 27103
Lipids; 16(9):655-662 1981

Herpes simplex virus type 2 was found to reduce the incorporation of phosphate, ethanolamine, and choline into phospholipids in infected human embryo fibroblasts. Suppression of phosphol ipid synthesis occurred during the time of max viral synthesis, and it was apparently secondary to virus-induced inhibition of host cell protein synthesis. (21 Refs)

9. IGG-FC-BINDING RECEPTORS IN CELLS ABORTIVELY INFECTED, OR TRANSFORMED, BY HUMAN CYTOMEGALOVIRUS.

Gonczol E, Boldogh I, Vaczi L
Inst. Microbiology, Univ. Medical Sch., P. O. B. 17, H-4012 Debreen, Hungary
Acta Microbiol Acad Sci Hung; 28(2):157-164 1981

IgG-Fc-binding membrane and cytoplasmic receptors were investigated in human embryonic fibroblast and hamster embryonic fibroblast cultures prepared, respectively, from human abortion material and Syrian golden hamster embryos, and also in cells transformed by human cytomegalovirus (HCMV). Cytoplasmic receptors were formed in abortively infected cells and similar receptors were formed on the cell surface of a low proportion (12-15%) of the cells infected either productively (human cells) or abortively (hamster cells). In the presence of cytosine arabinoside hydrochloride (ara-C), the receptors were formed in both the cytoplasm and cell membrane more readily than without ara-C. Cytoplasmic IgG-Fc receptors had formed in a very low proportion (2%) of the human cells and in a much higher proportion (65%) of the hamster cells while DNA synthesis was inhibited. IgG-Fc-binding receptors were transiently present in the cytoplasm and on the surface of cells being abortively infected by HCMV. The receptors were also present in cells transformed in vitro by HCMV (87-TRH-5 and CX-90-3B), as well as in cells of lines TSC-1 and TSC-2 from tumors induced by these cells. Thus, the indirect immunofluorescence test performed with sera containing no HCMV antibodies may give a positive reaction in the cytoplasm and/or cell membrane of the transformed cells. (18 Refs)

10. EFFECT OF CYTOMEGALOVIRUS ON ADULT HUMAN CHROMOSOMES.

Sakizli M, Luleci G, Gunalp A
Dept. Molecular Biology, Univ. Hacettepe, Ankara, Turkey
Acta Virol (Praha); 25(4):248-250 1981

The effects of cytomegalovirus infection on adult human chromosomes was studied in skin cell cultures. Chromosome Number 2 seemed to be affected specifically; chromosome abnormality distribution was independent of chromosome length. (Author abstract) (3 Refs)

VIRUS REPLICATION AND EXPRESSION

11. HERPES SIMPLEX VIRUS TYPES 1 AND 2 COMPLETELY HELP ADENOVIRUS-ASSOCIATED VIRUS REPLICATION.

Buller RM, Janik JE, Sebring ED, Rose JA
Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
J Virol; 40(1):241-247 1981

In addition to adenoviruses, which are capable of completely helping adenovirus-associated virus (AAV) multiplication, only herpesviruses are known to provide any AAV helper activity, but this activity has been thought to be partial (ie, AAV DNA, RNA, and protein syntheses are induced, but infectious particles are not assembled). In this study, however, we show that herpes simplex virus Type 1 (HSV-1) and Type 2 (HSV-2) are in fact complete AAV helpers and that AAV Type 2 (AAV2) infectivity yields can approach those obtained when coinfections are carried out with a helper adenovirus. AAV helper activity was demonstrated in KB cells with two HSV-1 strains (11124 and 17MP) and an HSV-2 strain (HG52). Each herpesvirus supported AAV2 multiplication with comparable efficiency. AAV2 multiplication was similarly efficient in HSV-1 coinfections of HeLa cells, whereas lower yields were obtained in HEp-2 and primary human embryonic kidney cells. HSV-1 also supported AAV-1 multiplication in HeLa cells but, at corresponding multiplicities of infection, AAV1 grew less efficiently than AAV2. Comparisons of the time courses of AAV2

DNA, RNA, and protein syntheses after coinfection with either adenovirus Type 5 or HSV-1 revealed that, in each case, the onset of synthesis and attainment of max synthesis rate occurred earlier in coinfections with HSV-1. These findings demonstrate the linkage of AAV macromolecular synthesis to an event(s) in the helper virus cycle. Aside from this temporal association, helper-related differences in AAV macromolecular synthesis were not apparent. (Author abstract) (22 Refs)

12. EFFECTS OF HYDROCORTISONE ON THE SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN P3HR-1 CELLS.

Prachova K, Roubal J
Dept. Experimental Virology, Inst. Sera and Vaccines, 181 03 Prague, Czechoslovakia
Acta Virol (Praha); 25(3):163-166 1981

Hydrocortisone was capable of enhancing the synthesis of Epstein-Barr virus antigens in producer P3HR-1 cells which had been induced with a 24-hr pulse of 5-iodo-2-deoxyuridine. The effect of hydrocortisone was time dependent, suggesting that an early step in the induction process, and not the antigen synthesis itself, was influenced by the drug. (Author abstract) (10 Refs)

13. DEGRADATION OF INTRACELLULAR DNA IN KB CELLS INFECTED WITH CYT MUTANTS OF HUMAN ADENOVIRUS TYPE 12.

Ezoe H, Lai Fatt RB, Mak S
Inst. Res. and Development, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan
J Virol; 40(1):20-27 1981

A group of mutants (cyt mutants) with much reduced oncogenicity was isolated from the highly oncogenic human adenovirus Type 12. These mutants induce extensive cellular destruction during lytic infection of human cells and produce low yields of virions. We report here that human KB cells infected with cyt mutants synthesized a reduced amount of viral DNA as compared with cells infected with the parental virus. Furthermore, the newly synthesized viral and cellular DNAs were extensively degraded in mutant-infected cells. Viral DNA was first synthesized as complete genome size, and most of it was degraded to subgenomic size within 6 hr after synthesis. This virus-induced DNA degradation function, as well as the low yield of virions, was prevented by co-infection with the parental virus. (Author abstract) (19 Refs)

14. PHORBOL ESTER-INDUCED EXPRESSION OF PRIMATE RETROVIRUSES.

Wunderlich V, Baumbach L, Sydow G
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 70/80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):615-622 1981

The 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of simian retroviruses of type C (BaEV, SSV) or type D (MPMV) and of a type D isolate derived from a human cell line (PMFV) was studied in four human cell lines (Tu 197, HEK, E1, and A 204). TPA caused a significant but transient increase in the virus production and cytomorphological changes in the cell lines Tu 197, HEK, and E1, but not in A 204. The stimulation of the virus production reaches its max on days 2-3, at which time the virus production was 15-30x higher than in controls. The optimal TPA concentration was 5-10 nanog/ml. Higher and lower concentrations had a much weaker stimulating effect. (25 Refs) (In GER)

VIRAL GENETICS AND MOLECULAR BIOLOGY

15. STRIKING SIMILARITIES ARE EXHIBITED BY TWO SMALL EPSTEIN-BARR VIRUS-ENCODED RIBONUCLEIC ACIDS AND THE ADENOVIRUS-ASSOCIATED RIBONUCLEIC ACIDS VAI AND VAII.

Rosa MD, Gottlieb E, Lerner MR, Steitz JA
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06510
Mol Cell Biol; 1(9):785-796 1981

The nucleotide sequence of the Epstein-Barr virus genome region coding two small RNAs (EBER 1 and EBER 2) was determined. Both EBERs are coded with a 707-base pair HaeIII/HaeIII fragment near the right-hand end of the EcoRI J/SstI fragment. The 5' terminal oligonucleotide for both is pppAGGAC. Both EBERS show heterogeneity at the 3' end. EBER 1 is 166 (167) nucleotides long. EBER 2 is 172+-1 nucleotides long. Both EBERs are transcribed from the same DNA strand; they are separated by 161 base pairs. The two EBERs show considerable homology, with the greatest in the areas of the 5' termini, around nucleotides 20 and 65, and near the 3' termini. Genes for both EBERs were transcribed by RNA polymerase III. Marked similarities exist between EBERs 1 and 2 and adenovirus-associated RNAs VAI and VAII. All are 160-170 nucleotides long and are transcribed in the same direction on their respective genome strands. Intragenic control regions for the four RNAs are homologous. All four RNAs form nucleoprotein complexes that precipitate with anti-La antibodies associated with systemic lupus erythematosus. Protein from uninfected HeLa cells conferred antigenicity on each of the four RNAs, indicating that antigenicity is conferred by host-cell rather than viral protein. (31 Refs)

16. IDENTIFICATION OF A VIRUS-SPECIFIC POLYPEPTIDE ASSOCIATED WITH A TRANSFORMING FRAGMENT (BGLII-N) OF HERPES SIMPLEX VIRUS TYPE 2 DNA.

Docherty JJ, Subak-Sharpe JH, Preston CM
Microbiology Program, Pennsylvania State Univ., University Park, PA, 16802
J Virol; 40(1):126-132 1981

The BglII N fragment of herpes simplex virus Type 2 (HSV-2) DNA (approx 0.58 to 0.63 map unit) was examined for encoded products. Using plasmid pGZ59, which consists of BglII-N cloned in pAT153, in conjunction with hybrid-arrested translation, mRNA selection, and in vitro protein synthesis, we found that the major translated product of this region has an approx mol wt of 37,800. By further mapping, coding sequences for this polypeptide were located within the region of BglII-N representing approx 0.58 to 0.61 genome map unit. To demonstrate immunological specificity, we used staphylococcal A protein immunoprecipitation with rabbit anti-HSV-1 or HSV-2 sera and antigens from HSV-1 or HSV-2 total mRNA translated in vitro and BglII-N-selected mRNA. The results show that the 37,800-dalton polypeptide has HSV-2 immunological specificity, as it is precipitated with anti-HSV-2 sera but not with anti-HSV-1 or control sera. (Author abstract) (20 Refs)

17. DEOXYRIBONUCLEASE I SENSITIVITY OF PLASMID GENOMES IN TERATOCARCINOMA-DERIVED STEM AND DIFFERENTIATED CELLS.

Huebner K, Linennbach A, Weidner S, Glenn G, Croce CM
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 78(8):5071-5075 1981

The DNase I (EC 3.1.21.1) sensitivities of the simian virus 40 (SV40) genome, the pBR322 genome, and the herpes simplex virus Type 1 thymidine kinase (HSV-1 tk) gene have been compared in teratocarcinoma-derived stem (12-1) and differentiated (12-1a) cell lines established by transfection of thymidine kinase (ATP: thymidine 5'-phosphotransferase, EC 2.7.1.21)-deficient F9 cells with DNA from a tripartite plasmid genome consisting of the pBR322 genome, the SV40 genome, and the HSV-1 tk gene. HSV-1 tk is present in both stem and differentiated cells; SV40 early proteins are present in differentiated cells but not in stem cells; the pBR322 genome is not expressed in either cell type. The SV40 and pBR322 genomes are more sensitive to DNase I digestion in stem cells than in differentiated cells, reflecting the DNase I-hypersensitivity of total stem-cell chromatin. The HSV-1 tk gene is the least sensitive to DNase I digestion in both cell types. (Author abstract) (30 Refs)

18. DOES SIMIAN VIRUS 40 T ANTIGEN UNWIND DNA?

Myers RM, Kligman M, Tjian R
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
J Biol Chem; 256(19):10156-10160 1981

Recently developed techniques allow rapid and accurate determination of protein-induced DNA unwinding. We have used such techniques to determine whether SV40 T antigen unwinds DNA. Assays were performed with purified wild type T antigen, D2 protein, and the SV80 T protein over a wide range of protein concentrations. Additionally, several DNA templates were used, including SV40 DNA, pBR322 DNA, and two plasmid DNAs containing one and three copies of the SV40 origin of replication. None of the purified proteins showed unwinding activity either in the presence or absence of ATP and Mg++. As a positive control, we found that unwinding of pBR322 DNA by Escherichia coli RNA polymerase occurred under identical assay conditions. Protein-DNA interactions that involve unwinding of the helix are sensitive to the superhelical density of the DNA. Using a filter binding assay, we found that the efficiency of the binding of T antigen to the viral origin of replication does not depend upon the topological state of the DNA. This result further supports our conclusion that SV40 T antigen is not an unwinding protein. (Author abstract) (32 Refs)

19. SEQUENTIAL TRANSCRIPTION-TRANSLATION OF SIMIAN VIRUS 40 BY USING MAMMALIAN CELL EXTRACTS.

Cepko CL, Hansen U, Handa H, Sharp PA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Mol Cell Biol; 1(10):919-931 1981

The expression of Simian virus 40 (SV40) was studied using the current technologies of recombinant DNA and in vitro transcription systems. The in vitro transcription of specific SV40 RNAs is described. A polypeptide comigrating with the 94K T antigen of SV40 was not present in products transcribed from Eco-RI-, PstI-, or TaqI-cleaved DNA. However, if a small fraction of the RNA transcribed from the Eco-RI-cleaved DNA had been processed by excision of the intervening sequences between 0.60 an 0.53 monitor units, synthesis of T (94K) would have been possible. Synthesis of the large T family of polypeptides is described. When the relative efficiencies of in vivo- and in vitro-synthetized RNA were quantitated, it was determined that in vitro small tumor antigen t messenger RNA (mRNA) is more efficiently translated than in vivo t mRNA. The translatability of the in vitro transcripts from the SV40 late regions was examined; the synthesis of the viral capsids VP1, VP2, and VP3 from RNA transcribed in vitro was studied. By using DNA templates cleaved within the late region, information concerning the identity of the transcripts that served as VP1, VP2, and VP3 messages was obtained. RNAs synthesized in vitro were fractionated by size to allow the direct identification of VP1, VP2, VP3, and t mRNAs. Other topics discussed include the efficiency of in vitro RNAs as messages, assay for RNA splicing, initiation at internal AUG codons, synthesis of polypeptides by minor transcripts (assay for proteins specified by complementary DNA clones), and lack of termination in the inhibition of translation. (32 Refs)

20. SV40 RECOMBINANT MOLECULES EXPRESS THE GENE ENCODING P21 TRANSFORMING PROTEIN OF HARVEY MURINE SARCOMA VIRUS.

Gruss P, Ellis RW, Shih TY, Konig M, Scolnick EM, Khoury G
Lab. Molecular Virology, NCI, Bethesda, MD, 20205
Nature; 293(5832):486-488 1981

Construction of the simian virus 40 (SV40)-Harvey murine sarcoma virus (Ha-MuSV) recombinants is described. The presence of a Ha-MuSV promoter element preceding the gene encoding p21 was shown. The new promoter element was found to be active not only in cells infected with recombinant but also in cells transformed with Ha-MuSV. (32 Refs)

21. DNA REPLICATION-MEDIATED RECOMBINATION OF MOLECULES OF ADENOVIRUS 2 DNA.

Wolgemuth DJ, Hsu M-T
(c/o Hsu) Dept. Molecular Cell Biology, Rockefeller Univ., New York, NY, 10021
Proc Natl Acad Sci USA; 78(8):5076-5080 1981

Molecules of adenovirus 2 DNA were isolated as nucleoprotein complexes late in infection of HeLa cells and examined by electron microscopy. Some were interpreted as representing intermediates in recombination events. The structures observed were consistent with predicted intermediates according to the model for genetic recombination proposed by Meselson and Radding and constitute physical evidence from animal cells in support of this model. (Author abstract) (16 Refs)

22. IDENTIFICATION AND CLONING OF ENDOGENOUS RETROVIRAL SEQUENCES PRESENT IN HUMAN DNA.

Martin MA, Bryan T, Rasheed S, Khan AS
DNA Recombinant Res. Unit, Office Scientific Director, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(8):4892-4896 1981

Using nonstringent annealing conditions and a 2.75-kilobase segment of cloned African green monkey DNA that specifically hybridizes to the proviruses of AKR ecotropic murine leukemia virus (MuLV) and baboon endogenous virus (BaEV) as a probe, we detected related sequences in three different preparations of human brain DNA fragments. The blot-hybridization pattern obtained with cleaved human DNA was similar to that previously reported for the interaction of MuLV cDNA and cleaved mouse DNA and suggested the presence of numerous copies of retrovirus-related sequences in the human genome. The labeled 2.75-kilobase fragment derived from cloned monkey DNA was used to screen a human DNA library in Charon 4A. One clone obtained hybridized to three contiguous MuLV- and BaEV-reactive fragments of the cloned monkey DNA and to multiple fragments of human DNA including a prominent 1.0-kilobase EcoRI fragment also present in the clone. (Author abstract) (37 Refs)

23. BABOON ENDOGENOUS VIRUS GENOME: MOLECULAR CLONING AND STRUCTURAL CHARACTERIZATION OF NONDEFECTIVE VIRAL GENOMES FROM DNA OF A BABOON CELL STRAIN.

Cohen M, Rein A, Stephens RM, O'Connell C, Gilden RV, Shure M, Nicolson MO, McAl lister RM, Davidson N
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(8):5207-5211 1981

Several heterogeneities in the baboon endogenous virus (BaEV) genomes that are present in the DNA of normal baboon tissues and the baboon cell strain BEF-3 have been described previously. To study these genomes, we cloned BaEV proviruses from BEF-3 cellular DNA into the lambda vector Charon 4A. Of the four full-length clones isolated, one was nondefective as determined by transfection. The sequence of a portion of this clone was found to code for amino acids 61-91 in the p30 region of the gag gene. This identification allowed us to align the restriction map with the BaEV genetic map. One heterogeneity, a BamHI site 2.4 kilobases (kb) from the proviral 5' end, was located close to the gag-pol junction; another, a BamHI site 1.4 kb from the 5' end of the genome, corresponded to the gag p30 coding sequence for amino acids 32-34; and a third, a Xho I site, was near the 3' end of the pol gene. To select the nondefective BaEV genomes from BEF-3 cells, we infected permissive cells with virus produced by BEF-3 cells and also transfected BEF-3 cellular DNA into permissive cells. The BaEV genomes in the permissive recipient cultures were then analyzed by restriction enzyme analysis. These nondefective genomes were found to be heterogeneous with respect to the gag-pol BamHI site and the Xho I site, but all were found to contain the BamHI site 1.4 kb from the 5' end of the genome. (Author abstract) (15 Refs)

IMMUNOLOGICAL STUDIES

24. T-CELL RESPONSE TO B-CELLS AND EPSTEIN-BARR VIRUS ANTIGENS IN INFECTIOUS MONONUCLEOSIS.

Klein E, Ernberg I, Masucci MG, Szigeti R, Wu YT, Masucci G, Svedmyr E
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Cancer Res; 41(11,part1):4210-4215 1981

After Epstein-Barr virus (EBV) infection in vivo, B-cells with latent virus infection persist indefinitely through life. These cells grow in vitro on explantation and can be established as immortal B-cell lines. To reconcile the unlimited growth potential in vitro with the maintenance of a low proportion of B-cells infected by EBV in vivo, a strict in vivo control mechanism has to be postulated. Certain aspects of this control are apparent when the primary infection is followed by infectious mononucleosis. This is characterized by lymphocytosis and the presence of activated T-cells. The T-cell proliferation is probably the manifestation of the immune response against EBV antigens. However, the reaction of T-cells upon encounter of B-blasts is also likely to contribute to the events. At present, it is difficult to detect an EBV-specific component in the action of the T-cells in the acute phase of mononucleosis exerted on B-cells. However, for the clinical course of the disease the activation of T-cells is important. The activated T-cells may control and also eliminate the B-cells infected by EBV. In addition to the immunity which develops during the disease, the immunoregulatory mechanism is likely to have a role in the inhibition of B-cell proliferation. (Author abstract) (52 Refs)

25. CELLULAR IMMUNE DEFECTS TO EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS IN YOUNG MALES.

Masucci MG, Szigeti R, Ernberg I, Masucci G, Klein G, Chessels J, Sieff C, Lie S, Glomstein A, Businco L, Henle W, Henle G, Pearson G, Sakamoto K, Purtilo DT
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4284-4291 1981

Three males with the X-linked lymphoproliferative syndrome (XLP) with hypo- or agammaglobulinemia following Epstein-Barr virus (EBV) infection and two males with the chronic mononucleosis syndrome were investigated for immune responses to EBV-determined antigens. Males with XLP showed profound cellular immune defects. Markedly diminished responses of natural killer cell and interferon-activated killer cell activities and impaired WBC migration inhibition responses to phytohemagglutinin were determined in patients with XLP. The two patients with chronic mononucleosis showed less severe defects. All patients showed partial or complete impairment of their EBV-specific immune responses as measured by WBC migration inhibition. EBV-specific antibodies were markedly diminished against EBV-associated nuclear antigen, early antigen, and viral capsid antigen in males with XLP. In contrast, patients with chronic mononucleosis had elevated antibodies to most EBV-specific antigens. Individuals with life-threatening EBV-induced lymphoproliferative disorders may exhibit multiple defective immune mechanisms against the virus. (Author abstract) (44 Refs)

26. CELL-MEDIATED IMMUNE REACTIONS IN THREE PATIENTS WITH MALIGNANT LYMPHOPROLIFERATIVE DISEASES IN REMISSION AND ABNORMALLY HIGH EPSTEIN-BARR VIRUS ANTIBODY TITERS.

Masucci MG, Szigeti R, Ernberg I, Bjorkholm M, Mellstedt H, Henle G, Henle W, Pearson G, Masucci G, Svedmyr E, Johansson B, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4292-4301 1981

Two patients with Hodgkin's disease in remission and one chronic lymphatic leukemia patient with extraordinarily high anti-Epstein-Barr virus (EBV) (viral capsid antigen) antibody titers (greater than 10,000) were selected to study a spectrum of cell-mediated immune responses, including natural killer, interferon-boosted killer, antibody-dependent lymphocytotoxicity, and T-cell-mediated reactions. The purpose was to compare these reactions in patients with immunosuppression and a high EBV load who can hold their EBV-carrying cells under control with the corresponding reactions in patients with EBV-carrying lymphoproliferative disease. In contrast to the latter group, the three patients of the present study showed a less profound and less general suppression of the immune responses. Multiple effector mechanisms probably safeguard against the proliferation of EBV-transformed B-cells. Clinically manifest EBV-carrying lymphoproliferative disease occurs only in very severe immunodeficiencies effecting multiple effectors. (Author abstract) (44 Refs)

27. LONG-TERM T-CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR VIRUS.

Rickinson AB, Moss DJ, Wallace LE, Rowe M, Misko IS, Epstein MA, Pope JH
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Cancer Res; 41(11,part1):4216-4221 1981

Experiments are reviewed that support the concept that a virus-induced lymphocyte-detected membrane antigen (LYDMA) elicits a cytotoxic T-cell response that controls persistent Epstein-Barr (EB) virus expression. Specific topics discussed are regression as an in vitro expression of T-cell memory, dependence of regression on cell concentration, EB virus-specific cytotoxic T cells as mediators of regression, LYDMA as the target antigen of effector T cells, reactivation of LYDMA-specific cytotoxicity by stimulation with autologous lymphoblastoid cells, HLA restriction of virus-specific T-cell cytotoxicity, and T-cell memory and the virus carrier state. (49 Refs)

28. EPSTEIN-BARR VIRUS-SPECIFIC SEROLOGY IN IMMUNOLOGICALLY COMPROMISED INDIVIDUALS.

Henle W, Henle G
Joseph Stokes, Jr., Res. Inst., Children's Hosp. of Philadelphia, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Cancer Res; 41(11,part1):4222-4225 1981

Since B-lymphocytes are targets and a continuing habitat of Epstein-Barr virus (EBV) and the cell-mediated immune system becomes secondarily involved, one may anticipate that primary and persistent EBV infections in immunologically compromised individuals take unusual courses. Depending on the immunological defect, the clinical, hematological, and serological responses to primary EBV infections may be more or less pronounced than in immunologically competent patients. Infectious mononucleosis has per se an immunosuppressive effect which may enhance a preexisting immune defect. The persistent latent viral carrier state which regularly ensues after the primary EBV infection may become decontrolled by immunosuppressive diseases or therapy, leading rarely to illnesses referable to the virus but often to increases in the titers of antibodies to viral capsid and early antigens and/or declines in the antibody titer to EBV-associated nuclear antigen. Absence or dysfunction of different WBC subpopulations may account for the differential changes in antibody patterns. (Author abstract) (42 Refs)

29. SEROEPIDEMIOLOGIC STUDIES IN HODGKIN'S DISEASE.

Kokosha LV, Lapin BA, Lebedev VN, Danilova NV, Arshba NN, Bologov VN
Lab. Experimental Oncology, Inst. Experimental Pathology and Therapy, Sukhumi, USSR
Probl Gematol Pereliv Krovi; 26(8):12-16 1981

To evaluate the possibility of horizontal transmission of Epstein-Barr virus (EBV), antibodies against capsid antigen of EBV were determined in 109 patients with Hodgkin's disease (HD) and in 67 relatives of 46 patients. High titers of antivirus antibodies were recorded in 70% of the patients with HD. The highest titers were recorded in the patients with lymphoid exhaustion (1:256, compared with 1:97 in lymphoid predominance and mixed cell variant, and 1:49 in nodular sclerosis). The titers of antibodies against EBV antigen in the relatives were significantly greater that that in healthy donors (1:69 and 1:6, respectively). (34 Refs) (In RUS)

30. HEPATITIS B VIRUS PROFILE OF HEPATOCELLULAR CARCINOMA IN THE PHILIPPINES.

Lingao AL, Domingo EO, Nishioka K
Immunology Section, Dept. Medicine, UP-PGH Medical Center, Taft Ave., Manila, Philippines
Cancer; 48(7):1590-1595 1981

The hepatitis B virus (HBV) profile was investigated in 104 age-grouped hepatocellular carcinoma (HCC) patients and 84 controls from the Philippines. The HCC-control percent positivities of the HBV parameters are: HBsAg: 70-18; anti-HBs: 25-37; anti-HBc: 94-35; HBeAg: 5-2; anti-HBe: 60-30; HBV exposure rate: 97-57; current infection: 80-31. Male HCC anti-HBs positivity is significantly lower than in controls. Female HCC patients' anti-HBs are also lower than controls, but this difference is not statistically significant. Simultaneous presence of HBsAg and anti-HBs was found only in male HCC patients. The mean anti-HBc titer of anti-HBs-positive HCC is higher than that of controls. That of HCC patients negative for both HBsAg and anti-HBs is also higher than the corresponding controls. Anti-HBe positivities of infected and noninfected but previously exposed HCC patients are not significantly different, in contrast to noninfected previously exposed controls whose anti-HBe is lower than those with current infection. The exposure rate prevalence of current infection, and the antibody responses to HBV of HCC patients suggest a close relationship between the two conditions in the Philippines. (Author abstract) (36 Refs)

31. DEMONSTRATION OF ANTIGENIC CROSS-REACTIVITY BETWEEN SIMIAN SARCOMA VIRUS (SSV) AND MASON-PFIZER MONKEY VIRUS (MPMV). BRIEF REPORT.

Micheel B
Central Inst. Cancer Res., Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Virol; 69(2):149-153 1981

The reaction of FITC-labeled simian sarcoma virus (SSV) with anti-SSV p30 antibodies conjugated to Sepharose beads is specifically blocked by incubation with antisera to different Type-C virus p30s and also by anti-MPMV p27 serum. (Author abstract) (14 Refs)

VIRAL STUDIES IN HUMAN CANCER

32. SUMMARY: SYMPOSIUM ON EPSTEIN-BARR VIRUS-INDUCED LYMPHOPROLIFERATIVE DISEASES IN IMMUNODEFICIENT PATIENTS.

Klein G, Purtilo D
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4302-4304 1981

The possibility that the X-linked lymphoproliferative syndrome, renal transplant lymphomas, and other lymphomas in immunodeficient patients originate in proliferating Epstein-Barr virus (EBV)-carrying lymphoid cells is discussed. Evidence for this association included the detection of EBV nuclear antigen (EBNA) in virus-transformed cells and changes in EBV antibody titers in immunodeficiency conditions. Defects of the T-cell system were associated with increased titers against EBV early and viral capsid antigens and decreased anti-EBNA titers. Chronic infectious mononucleosis patients and X-linked lymphoproliferative syndrome patients showed marked impairment of all effector mechanisms involved in the rejection of EBV-carrying cells. (23 Refs)

33. INTRODUCTION TO EPSTEIN-BARR VIRUS AND LYMPHOPROLIFERATIVE DISEASE IN IMMUNODEFICIENT INDIVIDUALS.

Purtilo DT, Klein G
Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Res; 41(11,part1):4209 1981

Attention is directed to accompanying articles on the possible roles of Epstein-Barr virus (EBV) and immunodeficiency in lymphoproliferative diseases (LPD). The authors have sought to develop criteria for establishing involvement or noninvolvement of EBV in LPD in immunodeficient patients. (11 Refs)

34. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY CLINICAL, VIROLOGICAL, AND IMMUNOPATHOLOGICAL STUDIES.

Purtilo DT, Sakamoto K, Saemundsen AK, Sullivan JL, Synnerholm AC, Anvret M, Pritchard J, Sloper C, Sieff C, Pincott J, Pachman L, Rich K, Cruzi F, Cornet JA, Collins R, Barnes N, Knight J, Sandstedt B, Klein G
Dept. Pathology Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Res; 41(11,part1):4226-4236 1981

Multiple methods, pedigree analysis, clinical evaluation, and Epstein-Barr virus (EBV)-specific serology, EBV DNA hybridization of tissues to probe for viral genome, staining of touch imprints for EBV nuclear-associated antigen, establishment of spontaneous infected B-cell lines from peripheral blood or tissues, examination of peripheral blood smears, and hematopathology studies, were used to study seven patients with the X-linked lymphoproliferative syndrome and seven additional patients with life-threatening EBV-associated diseases. These studies demonstrated EBV in the tissues of all 14 patients and immunodeficient antibody responses to EBV were documented. This virus can produce various life-threatening lymphoproliferative diseases in a variety of immunodeficient patients. (Author abstract) (35 Refs)

35. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY EPSTEIN-BARR VIRUS COMPLEMENTARY RNA/DNA AND VIRAL DNA/DNA HYBRIDIZATION.

Saemundsen AK, Purtilo DT, Sakamoto K, Sulllivan JL, Synnerholm AC, Hanto D, Simmons R, Anvret M, Collins R, Klein G
Dept. Tumor Biology, Karolinska Inst., 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4237-4242 1981

Tissues from patients thought to have Epstein-Barr virus (EBV)-induced lymphoproliferative diseases were probed for EBV genomes using two independent hybridization techniques. Tissues from six patients with the X-linked lymphoproliferative syndrome, all five renal allograft recipients with immunoblastic sarcoma, and eight patients with diverse types of immunodeficiency and lymphoproliferative diseases such as fatal infectious mononucleosis or malignant lymphoma associated with antecedent immunodeficiency contained significant numbers of EBV genome equivalents per cell. The use of two hybridization probes is recommended to confirm the presence of EBV genomes. The finding of significant numbers of EBV genomes in tissues from patients with immunodeficiency suggests that EBV is the etiological agent of the associated lymphoproliferative diseases. (Author abstract) (53 Refs)

36. DIVERSE FAMILIAL MALIGNANT TUMORS AND EPSTEIN-BARR VIRUS.

Purtilo DT, Liao SA, Sakamoto K, Snyder LM, DeFlorio D, Bhawan J, Paquin L, Yang JP, Hutt-Fletcher LM, Muralidharan K, Raffa P, Saemundsen AK, Klein G
Dept. Pathology, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Res; 41(11,part1):4248-4252 1981

Continued monitoring of a family for new malignant tumors has revealed diverse immunological and neoplastic disorders during a 15-yr period. In 1966, the proband developed lymphoma. In 1975, his antibody titers to Epstein-Barr virus (EBV) became elevated, an again, he developed a malignant lymphoma. He also had borderline hypo-Ig A, died of glioblastoma multiforme in 1977, and at autopsy, had adenomatous colonic polyps. His eldest brother has normal Ig levels, but developed immune thrombocytopenia in 1973 and had elevated EBV antibody titers in 1980. Another brother had hypo-Ig A, thymoma in 1965, and adenomas and adenocarcinoma of the colon. Two other brothers succumbed to glioblastoma in 1968 and 1969. The father of the proband had bronchiectasis in 1952, hypo-Ig M documented in 1972, and elevated EBV antibody titers 5 yr preceding development of a malignant lymphoma. The latter contained 10 EBV genome equivalents/cell by EBV viral DNA/DNA reassociation kinetics analysis. The proband's grandmother had died of an Ig G-secreting myeloma in 1977, and his grandfather had borderline low Ig M, elevated EBV antibody titers, and hypopharyngeal carcinoma in 1980. Predisposition to oncogenesis in this family was probably inherited. (Author abstract) (26 Refs)

37. EPSTEIN-BARR VIRUS IN A MALIGNANT LYMPHOPROLIFERATIVE DISORDER OF B-CELLS OCCURRING AFTER THYMIC EPITHELIAL TRANSPLANTATION FOR COMBINED IMMUNODEFICIENCY.

Reece ER, Gartner JG, Seemayer TA, Joncas JH, Pagano JS
Dept. Allergy and Clinical Immunology, Montreal Children's Hosp. Res. Inst., McGill Univ., Montreal, Quebec, H3H 1P3, Canada
Cancer Res; 41(11,part1):4243-4247 1981

A fatal disseminated polyclonal malignant lymphoproliferative disorder of B-cells (immunoblastic sarcoma) developed shortly after a second thymic epithelial peritoneal implant in a 5-yr-old girl with combined immunodeficiency. The immunodeficiency was characterized by low T-cell numbers and function, very low levels of thymic hormone, dysgammaglobulinemia, and an inability to mount a primary antibody or cell-mediated response to new antigens. At necropsy, the thymus fulfilled morphological criteria for thymic dysplasia. Epstein-Barr virus (EBV) antigen and DNA were identified in neoplastic infiltrates in the lymph nodes and thymus by immunofluorescence for the EBV nuclear antigen and by EBV-specific complementary RNA/DNA hybridization. No antibodies to nuclear antigen, early antigen, or viral capsid antigen of EBV were identified in the serum. The concurrence of these events suggests that the thymic epithelial implant itself may have been instrumental in the pathogenesis of this neoplasm. It is proposed that the thymus may have provided factors which indirectly potentiated the proliferation of EBV-infected B-cells, possibly by induction of nonspecific T-helper cells and perhaps through other thymic humoral factors. It is suggested that some forms of immunoblastic sarcoma, even when polyclonal, and especially those which arise in immunocompromised hosts, may, in some instances, represent an opportunistic form of EBV-induced B-cell neoplasia. (Author abstract) (39 Refs)

38. CLINICAL SPECTRUM OF LYMPHOPROLIFERATIVE DISORDERS IN RENAL TRANSPLANT RECIPIENTS AND EVIDENCE FOR THE ROLE OF EPSTEIN-BARR VIRUS.

Hanto DW, Frizzera G, Purtilo DT, Sakamoto K, Sullivan JL, Saemundsen AK, Klein G, Simmons RL, Najarian JS
Dept. Surgery, Univ. Minnesota, Mayo Memorial Building, 420 Delaware St. South East, Minneapolis, MN, 55455
Cancer Res; 41(11,part1):4253-4261 1981

Six renal transplant recipients with abnormal lymphoproliferative disorders were studied in an attempt to define their clinical features and the role of Epstein-Barr virus (EBV) in their pathogenesis. Patients were either teenage (3) or in the sixth decade (3). The younger patients presented an av of 3 mo after transplantation with fever, sore throat, and lymphadenopathy; had been markedly immunosuppressed; frequently had preceding or concomitant cytomegalovirus infections; and two of three had a rapidly fatal course. The older patients presented an av of 5 yr after transplantation while on maintenance immunosuppressive drugs; in two of three cases with an oropharyngeal tumor; and had a more indolent, but frequently fatal, clinical course. The most frequent sites of biopsy-proven involvement in these patients were lymph nodes (3), the oropharynx (3), liver (3), bone marrow (3), transplanted kidney (3), colon (2), and central nervous system (2). EBV-specific antibody titers including anti-viral capsid antigen IgG, anti-viral capsid antigen IgM, anti-early antigen, and anti-Epstein-Barr nuclear antigen were serially measured in all patients. Four patients demonstrated serological evidence of a primary (1) or reactivation (3) EBV infection. No patient had significant changes in anti-early antigen or anti-Epstein-Barr nuclear antigen titers. All three patients tested for oropharyngeal shedding of EBV were positive. A touch imprint of one tumor was stained for the presence of Epstein-Barr nuclear antigen, and a majority of cells were positive. EBV complementary RNA/DNA filter hybridization and/or viral DNA/DNA reassociation analysis performed on tumor biopsy specimens in five patients demonstrated multiple EBV genome equivalents per cell in all eight specimens tested. Clinical, pathological, serological, and molecular hybridization studies provide substantial evidence that EBV was the cause of these lymphoproliferative disorders occurring after renal transplantation. Impaired host defenses allow the EBV-transformed B-lymphocytes to escape normal control mechanisms. This impairment is variable and influenced by many factors resulting in the observed spectrum of disease. Cytogenetic changes, however, may also be important. (Author abstract) (45 Refs)

39. EPSTEIN-BARR VIRUS INFECTION AND NEOPLASIA.

Sprinkle PM, Veltri RW
Dept. Otolaryngology, West Virginia Univ., Morgantown, WV
Otolaryngol Head Neck Surg; 89(4):542-544 1981

Conclusive serological data of activation of Epstein-Barr virus (EBV) is reported showing persistently elevated early antigen (EA) titers prior to and following malignant transformation in a 6-yr-old boy. Heterophil-negative EBV disease characterized by lymphadenopathy and recurrent tonsillitis developed in the child 1 mo after his sister died with heterophil-negative infectious mononucleosis. Epstein-Barr nuclear antigen (EBNA) and EA were detected in many B-lymphocytes present in each of the same tissue specimens. One yr later, rebiopsy of the cervical nodes revealed typical Hodgkin's disease. EBNA and EA were found in hilar and celiac lymph nodes as well as in splenic lymphocytes. Serum antibody study demonstrated a 1:640 EA and 1:2,560 viral capsid antigen-IgG specific antibody to their EBV-coded antigens. Before and after the diagnosis of Hodgkin's disease, however, the patient's EA titers were persistently elevated and remained so. The child was alive with a poor prognosis after multiple chemotherapy courses and two courses of radiotherapy. The child's mother died in the interim with undifferentiated lymphoma. (16 Refs)

40. INFECTIOUS MONONUCLEOSIS AND ACUTE LEUKEMIA.

Rosner F, Grunwald HW
Dept. Medicine, Long Island Jewish-Hillside Medical Center, 82-68 164 St., Jamaica, NY, 11432
JAMA; 246(16):1783-1784 1981

Relationship between infectious mononucleosis and acute leukemia is discussed with respect to 26 reported cases in which the diseases coexisted. No clear relationship was found between Epstein-Barr virus, infectious mononucleosis, and acute leukemia; future cell typing of forms of acute leukemia other than Burkitt's lymphoma may allow detection of subtypes with distinct Epstein-Barr virus receptors, providing some possible linkage between the development of leukemia and that of infectious mononucleosis. (21 Refs)

41. EBV-POSITIVE BURKITT'S LYMPHOMA FROM ALGERIA, WITH A THREE-WAY REARRANGEMENT INVOLVING CHROMOSOMES 2, 8 AND 9.

Philip T, Lenoir GM, Fraisse J, Philip I, Bertoglio J, Ladjaj S, Bertrand S, Brunat-Mentigny M
Service de Pediatrie, Centre Leon-Berard, 28, rue Laennec, 69373 Lyon cedex 2, France
Int J Cancer; 28(4):417-420 1981

Burkitt's lymphoma was diagnosed in a male Algerian child presenting with abdominal and jaw tumors. Viral studies revealed that this non-endemic case was associated with the Epstein-Barr virus. Cytogenetic examination of tumor cells showed a complex three-way rearrangement involving chromosomes 2, 8 and 9. Our report indicates that, in Burkitt's lymphoma, not only simple but also complex translocations involving chromosome 8 may arise. This finding in a North African case emphasizes the need for more detailed study of the clinical, virological and cytogenetic features of Burkitt's lymphoma throughout the world. (Author abstract) (36 Refs)

42. A NEW VIEW OF THE ETIOLOGY OF NASOPHARYNGEAL CARCINOMA.

Hirayama T, Ito Y
(c/o Ito) Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Prev Med; 10(5):614-622 1981

Epidemiological studies showed a high incidence of nasopharyngeal carcinoma (NPC) in southern regions of China. Also found in these regions are plants of the Euphorbiaceae family, including Croton tiglium (the source of croton oil) and other species used as herbal drugs. Interaction of herbal drugs and anti-Epstein-Barr virus (EBV) titers was noted. Use of the herbal drugs was related to nasal infection by microbes such as Fusobacterium. The combined effects of drug use and EBV induction were synergistic rather than additive. Fusobacteria in culture produced n-butyric acid, which had a low, but definite EBV-inducing activity in human lymphoblastoid P3HR-1 cells. Combined treatment with nanog concentrations of croton oil and n-butyrate produced marked increase in EBV antigens in EBV genome-carrying P3HR-1 and Raji cells. Apparently EBV is induced and activated by the combination of bacterial fatty acid and herbal oils. It is suggested that the activated EBV then initiates steps resulting in NPC. (33 Refs)

43. HERPESVIRUS TYPE 2 IN ADENOCARCINOMA OF THE UTERINE CERVIX: A POSSIBLE ASSOCIATION.

Menczer J, Yaron-Schiffer O, Leventon-Kriss S, Modan M, Modan B
Dept. Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Israel
Cancer; 48(7):1497-1499 1981

Sera from 16 Jewish patients with histologically confirmed adenocarcinoma of the uterine cervix (AUC) and 32 control subjects matched by age and ethnic origin were examined for herpesvirus Type 1 (HSV-1) and Type 2 (HSV-2) neutralizing antibodies. Titers were determined by means of the quantitative plaque reduction neutralization test on VERO cell monolayers, using HSV-1 strain VR3 and HSV-2 strain. Significantly increased levels of antibodies against both virus strains were found in the AUC patients as compared with the controls. The trends in the AUC series resembled those in a previous similar case-control study of squamous cell carcinoma of the uterine cervix (SUC). Thus, the previously observed association between HSV-2 and SUC is true for AUC as well, despite differences in the clinical and epidemiologic characteristics of the two malignancies. (Author abstract) (9 Refs)

44. KAPOSI'S SARCOMA. IV. DETECTION OF CMV DNA, CMV RNA AND CMNA IN TUMOR BIOPSIES.

Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G
(c/o Huang) Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514
Int J Cancer; 28(4):469-474 1981

In order to determine whether human cytomegalovirus-(CMV) DNA homologous sequences as well as CMV-specific RNA(s) and antigen(s) exist in tumor biopsies of Kaposi's sarcoma (KS) DNA-DNA reassociation, RNA-DNA in situ cytohybridization and anticomplement immunofluorescence test (ACIF) tests were applied. Three of 10 DNAs extracted from Kaposi sarcoma biopsies contained DNA sequences homologous to radioactively labeled human CMV DNA probe. The amount of CMV DNA in these sarcoma tissues was calculated to range from 0.7 to 1 genome equivalent per diploid cell. The presence of virus-specific RNA was also demonstrated in sections from 5 of 10 tumor biopsies. CMV-determined nuclear antigen(s) (CMNA) present in variable degrees were also demonstrated. In contrast, we could not detect any herpes simple virus type II (HSV-2) or Epstein-Barr virus (EBV) DNA sequences in DNA of these tumor biopsies. Furthermore, there were no detectable HSV-2 or EBV-specific RNA or virus-specific antigens in sections of these biopsies. These results provide new lines of evidence for the relationship between CMV and Kaposi's sarcoma. (Author abstract) (34 Refs)

45. ETIOLOGICAL IMPLICATIONS ON KAPOSI'S SARCOMA.

Giraldo G, Beth E, Kyalwazi SK
Natl. Cancer Inst. 'Fondazione Pascale', Naples, Italy
Antibiot Chemother; 29:12-29 1981

Multidisciplinary study of 176 cases of Kaposi's sarcoma (KS) was conducted during 1971-1979. Biopsy specimens and sera from KS patients and corresponding controls were collected within five different African Cancer Centers in areas of high and moderate KS incidence. Samples were also collected in various hospitals in areas of France with a low incidence of KS. African KS patients had high antibody titers to cytomegalovirus (CMV), but they were not significantly different from controls in the same regions. A specific serological association of European and American KS with CMV was established. CMV-related antigens were detected in 22% of tumor biopsies and in early passages of cell cultures derived from them. CMV-DNA sequences have been detected in tumor biopsies. Strain K9V CMV has been isolated in a KS-derived tissue culture. In vitro, cells infected with K9V have some of the features of cells transformed by other oncogenic CMV strains. In vivo, K9V induced a fatal lymphoid disease in old world monkeys. Clusters of KS have been observed in the West Nile District of Uganda. A significantly higher incidence of second primary tumor, particularly of the lymphoreticular system, has been observed in KS patients. (32 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

46. STEROIDS INHIBIT TUMOR PROMOTING AGENT INDUCED EPSTEIN-BARR VIRUS EARLY ANTIGENS IN RAJI CELLS.

Sundar SK, Ablashi DV, Armstrong GR, Zipkin M, Faggioni A, Levine PH
Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Int J Cancer; 28(4):503-507 1981

Four steroids and one protease inhibitor were evaluated for their effects on 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced and Epstein-Barr virus-induced early antigens (EBV-EA) in Raji cells. Continuous treatment with dexamethasone, prednisolone, hydrocortisone and cortisone inhibited TPA-induced EBV-EA to varying degrees, but the protease inhibitor N-alpha-p-tosyl L-lysine chloromethyl ketone-HCl (TLCK) had no significant effect. None of the agents tested inhibited EBV-induced EA. In addition, the effect of the steroids was reversible since the removal of these agents resulted in recovery of the percentage of EBV-EA-positive cells in TPA-treated cultures. These results were in agreement with the in vivo experiments of other investigators, who demonstrated inhibition of tumor promotion with steroids. Since TLCK failed to inhibit TPA-induced EA, it is unlikely that induction of EA by TPA is the result of production of proteases. (Author abstract) (36 Refs)

OTHER RELATED STUDIES

47. FATAL EPSTEIN-BARR VIRUS INFECTION IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN REMISSION.

Look AT, Naegele RF, Callihan T, Herrod HG, Henle W
Div. Hematology Oncology, St. Jude Children's Res. Hosp., P.O. Box 318, Memphis, TN, 38101
Cancer Res; 41(11,part1):4280-4283 1981

A 9-yr-old white boy developed a fatal primary Epstein-Barr virus (EBV) infection while receiving chemotherapy for acute lymphoblastic leukemia in remission. Histopathological findings at the height of the proliferative phase of the illness were compatible with a virally induced hemophagocytic syndrome. The infection spontaneously converted to complete aplasia of the bone marrow and lymph nodes. Serological studies disclosed that the patient had no antibodies to EBV prior to the infection, but during the acute phase he showed a spectrum and titers of antibodies to EBV-specific antigens characteristic of a current primary EBV infection. A lymph node biopsy obtained 5 wk after onset revealed Epstein-Barr nuclear antigen in approx 50% of the cells. The boy's condition deteriorated rapidly, with disseminated candidiasis resulting in cardiorespiratory failure and death. Lymph nodes obtained at autopsy no longer contained Epstein-Barr nuclear antigen-positive cells. (Author abstract) (24 Refs)

48. UV-INDUCED REVERSION OF ADENOVIRUS 5TS2 INFECTING HUMAN CELLS.

Day RS, Ziolkowski CH
Nucleic Acids Section, LMC, DCCP, NCI, NIH, Bldg. 37, Rm. 3C23, Bethesda, MD, 20205
Photochem Photobiol; 34(3):403-406 1981

Among the progeny produced by UV-irradiated adenovirus 5ts2 when infecting either A498 (human kidney tumor) or CRL1187 (normal human fibroblast) strains at 32 C were a certain number (UV-fluence dependent) of revertants able to grow at 39 C. Within experimental error, the induced reversion frequency was independent of whether or not the cells received UV (5 J/m2) 20 hr prior to infection, indicating that induced error-prone repair was not observed in these experiments. (Author abstract) (19 Refs)

49. AUGMENTATION IN THE INFECTIVITY OF SV40 VIRUS DNA BY AMPHOTERICIN B METHYL ESTER. BRIEF REPORT.

Borden EC, McBain JA, Martin J, Walker D
Dept. Human Oncology, Univ. Wisconsin Clinical Sciences Center, Madison, WI, 53792
Arch Virol; 69(2):161-165 1981

The methyl ester of amphotericin B (100 ug/ml) enhanced the infectivity of SV40 virus DNA for CV-1 cells up to 300-fold. Amphotericin B methyl ester may prove useful for augmenting cellular penetration of macromolecules and for probing biological mechanisms. (Author abstract) (15 Refs)

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HE 20.3173/2:

VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. LATE NONSTRUCTURAL 100,000-AND 33,000-DALTON PROTEINS OF ADENOVIRUS TYPE 2: II. IMMUNOLOGICAL AND PROTEIN CHEMICAL ANALYSIS.

Gambke C, Deppert W
Friedrich Miescher Inst., CH-4002 Basel, Switzerland
J Virol; 40(2):594-598 1981

For an immunological analysis of the late adenovirus Type 2 nonstructural 100,000-dalton (100K) and 33K proteins, we prepared antisera against sodium dodecyl sulfate-denatured, gel-purified 100K and 33K proteins. These antisera were tested for potential cross-reactivity, since according to a previous report these two proteins exhibit extensive amino acid homologies. However, immunoprecipitations of 100K and 33K proteins, as well as a sensitive immune replica technique, did not reveal any immunological relationship between these proteins. Therefore, using fingerprint peptide analysis, we investigated the structural relationship between 100K and 33K proteins labeled with a 14C-amino acid mixture or with [14C]proline after digestion with trypsin. We detected only minor, if any, amino acid homologies, indicating that the 100K and 33K proteins are not structurally related. (Author abstract) (21 Refs)

2. ANATOMY OF ONCOGENIC TUPAIA HERPESVIRUSES ISOLATED FROM A MALIGNANT LYMPHOMA AND A HODGKIN'S SARCOMA (MEETING ABSTRACT).

Darai G, Matz B, Flugel RM, Delius H
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Tupaia (the tree shrew), a member of the family Tupaiidae, is regarded as one of the prosimians that most bridges the gap between insectivores and primates. The isolation and characterization of Tupaia Herpesviruses has been reported. Tupaia Herpesviruses (THV) were efficiently propagated, plaque-purified and cloned on tupaia embryonic fibroblasts. The characterization of the DNA of these Tupaia Herpesviruses was studied. The DNA of THV-2, which was isolated from malignant lymphoma and THV-3, which was isolated from a Hodgkin's sarcoma of tupaia were analyzed in detail. The viral DNAs were cleaved with different restriction endonucleases, and the cleavage sites of Hind III and Eco RI enzymes on THV-2 and 3 DNA were determined. The mol wt of THV DNAs was determined by electron microscopic measurement of the contour length of the DNA, which resulted in 133x10(6) for THV-2 and 130x10(6) for THV-3. Single-stranded DNA of THV was prepared for electron-microscopy by heating the viral DNA in formamide and isolating the single-strands from agarose gel. It was found that single-stranded THV DNA does not display any extended stem-loop structures. With respect to the structure of THV genomes, the Tupaia Herpesviruses are unique when compared to the DNAs of other known herpesviruses from different species. This conclusion was verified by electron microscopic examination of single-stranded THV-DNA under conditions favoring intra-strand hybridization. Self-annealed single strands of THV-DNA did not form stem-loop structures. This result rules out the existence of isomeric forms of THV DNAs. (3 Refs)

3. ALTERNATIVE INTERACTIONS OF THE SV40 A PROTEIN WITH DNA.

Tegtmeyer P, Andersen B, Shaw SB, Wilson VG
Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11794
Virology; 115(1):75-87 1981

We have characterized the DNA binding properties of SV40 A protein (T antigen) from permissive cells. The viral protein protects 110-to 115-, 60-to 65-, 40-to 45-, and 30-to 35-bp fragments of SV40 DNA from an excess of DNase I. The 60-to 65-bp fragment extends some 30-35 bp to either side of the BglI site at the origin of replication. DNase footprinting confirms the location of this binding region and shows that it is the most completely protected DNA binding site under our conditions. The A protein selectively recognizes the 60-to 65-bp origin fragment in the complete absence of adjacent DNA and binds to it in three alternative ways that protect 60-65, 40-45, or 30-35 bp from nuclease. Thus these three interactions with isolated origins recapitulate the binding of viral protein to intact SV40 DNA. We propose that the alternative interactions of SV40 A protein with the 60-to 65-bp origin fragment may represent three different conformational alignments of protein with DNA rather than a simple repetition of a single kind of binding interaction. Viral protein also protect pBR322 and lambda phage DNA from nuclease to a limited extent. Similar interactions could possibly alter the function of DNA control regions of host cells. (Author abstract) (15 Refs)

4. BINDING OF DEPHOSPHORYLATED A PROTEIN TO SV40 DNA.

Shaw SB, Tegtmeyer P
(c/o Tegtmeyer) Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11794
Virology; 115(1):88-96 1981

We have examined the role of SV40 A protein (T antigen) phosphorylation in the specific binding of the protein to SV40 DNA using protein that was dephosphorylated in vitro. Alkaline phosphatase removed more than 75% of the phosphate radiolabel associated with the A protein. Most of the phosphoserine residues were sensitive to the enzyme while most of the phosphothreonine residues were resistant. Phosphopeptide mapping of the dephosphorylated protein demonstrated that the phosphate groups at individual sites were either highly sensitive or highly resistant to the phosphatase. Thus, enzymatically dephosphorylated A protein provides a useful probe for analysis of the function of specific phosphorylation sites. Dephosphorylated A protein, like untreated A protein, preferentially bound a restriction fragment of SV40 DNA that contains the origin of DNA replication and sequences involved in transcriptional control. The binding was characterized further using a DNase protection assay and DNase footprinting. Dephosphorylated A protein protected SV40 DNA in a manner that was indistinguishable from that of untreated protein. The effects of A protein concentration and salt treatment on binding were the same for phosphatase-treated and control untreated A protein under the conditions of our assay. These results suggest that the location, alignment, and affinity of binding are unaffected by dephosphorylation. We conclude that phosphorylation at the majority of the phosphoserine sites is not directly involved in the regulation of site-specific recognition and binding of the A protein to SV40 DNA. (Author abstract) (23 Refs)

5. THE V-SIS TRANSFORMING GENE OF SIMIAN SARCOMA VIRUS IS A NEW ONC GENE OF PRIMATE ORIGIN.

Wong-Staal F, Dalla Favera R, Gelmann EP, Manzari V, Szala S, Josephs SF, Gallo RC
Lab. Tumor Biology, NCI, Bethesda, MD, 20205
Nature; 294(5838):273-275 1981

Studies on the cloned simian sarcoma virus (SSV) genome are presented which show that a 1.2-kilobase transformation-specific viral onc gene, v-sis, is distinct from other genes and is derived from a woolly monkey which had previously co-habited with a gibbon before it developed sarcoma. A PstI-PstI fragment of the SSV genome that contains approx 250 base pairs (bp) of 5' v-sis sequences and 900 bp of nondefective helper virus (SSAV)-derived sequences were subcloned into the bacteriophage M13. The single-stranded phage DNA was then partially digested with DNase and terminally labeled with 32P. Labeled DNA was hybridized to cellular DNA from tissues of different animals and resultant hybrids were assayed by their resistance to S1 nuclease. Primate DNA hybridized significantly better than DNA from non-primates. Among primates, highest homology was obtained with woolly monkey DNA. The SSAV genome had no detectable homology to primate DNA and its distant homology to rodent DNA could only be monitored by non-stringent hybridization conditions. It is concluded that v-sis originated from woolly monkey DNA. The close relatedness of SSAV to different gibbon ape leukemia virus isolates and the revelation that the woolly monkey that yielded SSV/SSAV co-habited with a gibbon before it developed sarcoma suggests that SSAV was transmitted from gibbon to woolly monkey during that period, and that in a single infection event, SSAV had recovered an onc gene from woolly monkey to generate SSV. To date this is the only onc gene of primate origin. (24 Refs)

6. ISOLATION OF A NEW TYPE C RETROVIRUS (HTLV) IN PRIMARY UNCULTURED CELLS OF A PATIENT WITH SEZARY T-CELL LEUKAEMIA.

Poiesz BJ, Ruscetti FW, Reitz MS, Kalyanaraman VS, Gallo RC
Lab. Tumor Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 294(5838):268-271 1981

A new type C retrovirus (HTLV-mb) has been isolated from a cell line from a 64-yr-old black female patient, MB, with the leukemic phase of Sezary syndrome. This cell line, CTCL-2 was established with use of partially purified T-cell growth factor from a sample of her peripheral blood. These cells have produced typical type C particles from the earliest passage studied (passage 2) but only after induction with 5-iodo-2'-deoxyuridine. The fractions containing HTLV-mb particles were identified by electron microscop y and by assaying for reverse transcriptase. Proteins and nucleic acid of HTLV were also identified in the fresh, uncultured, Sezary leukemic blood cells from which the second isolate was obtained. Analysis of the proteins and nucleic acids of this retrovirus isolate indicate close relationship to HTLV-cr, a retrovirus recently isolated and characterized from a patient with cutaneous T-cell lymphoma (mycosis fungoides) but distinct from known animal retroviruses. (23 Refs)

7. GROWTH OF HUMAN NORMAL AND LEUKEMIC T CELLS: T-CELL GROWTH FACTOR (TCGF) AND THE ISOLATION OF A NEW CLASS OF RNA TUMOR VIRUSES (HTLV).

Gallo RC, De The, Lajtha L, Van Bekkum DW, McCulloch EA, Greaves MJ, Seligmann M, Brecher G, Shohet SB, Bessis M, Sachs L
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Blood Cells; 7(2):313-329 1981

Previous studies have indicated that T-cell growth factor (TCGF) is the physiological growth promoter in the immune response of T-lymphocytes, acting as the second signal (after antigen) in the immune response. A summary is presented of information on proliferation of normal T-cells in a previously described liquid suspension culture and proliferation of several new cell lines from patients with particular types of T-cell leukemias and lymphomas. Information on the new type-C virus designated HTLV is also summarized. Neoplastic T cells from patients with cutaneous T-cell leukemias and and lymphomas, eg Sezary syndrome and mycosis fungoides, were grown routinely with the use of purified TCGF free of phytohemagglutinin and of lymphokines other than TCGF. The neoplastic T cells responded directly to TCGF without prior in vitro activation with antigen or lectin as is necessary with normal T cells. Thus, transformed mature T cells already express TCGF receptors. HTLV were isolated from some of these new cell lines. Evidence is presented to indicate these may be the first unambiguous isolates of RNA tumor viruses from humans. These new viruses are easily distinguished from all previously isolated viruses from animals. Antibodies in sera of some patients with these diseases specifically react with proteins of these viruses. (11 Refs)

8. A VIRUS ASSOCIATED WITH HUMAN ADULT T-CELL LEUKAEMIA.

Weiss R
Inst. Cancer Res., London, England
Nature; 294(5838):212 1981

Recent virological, serological and epidemiological evidence strongly indicates that a newly discovered retrovirus is the etiological agent of certain types of adult T-cell lymphoma/leukemia. The virological evidence first came from RC Gallo's laboratory at the US NCI where the retrovirus was isolated from a T-lymphoma cell line established in culture from a patient with mycosis fungoides. In this issue of Nature Poiesz et al report the isolation of a similar virus from a patient with Sezary syndrome, while Kalyanaraman et al show that the two patients' sera (and that of a patient's spouse) contain antibodies which specifically react with the major core protein of the virus. Mycosis fungoides and Sezary syndrome are clinical variants of cutaneous T-cell lymphoma and leukemia, respectively, that occur as rare diseases in adults. The retrovirus particles produced by these tumors are not evident until the tumor cells are grown in culture, although a second biopsy from the first patient released virus within 24 hr of its being placed in culture. Until 5 yr ago it was very difficult to maintain normal or malignant T cells in culture; however, a specific T-cell growth factor (TCGF) discovered in Gallo's laboratory enables T cells to proliferate in vitro for long periods, and this aided the detection of the virus. (Author abstract) (12 Refs)

9. RETROVIRUS PARTICLE PRODUCTION IN THREE OF FOUR HUMAN TERATOCARCINOMA CELL LINES.

Lower J, Lower R, Stegmann J, Frank H, Kurth R
No affiliation given
Haematol Blood Transfus; 26:541-544 1981

Cells lines (GH, HL, Tera-1, and Tera-2) derived from human teratocarcinomas were studied for virus expression. The initial search for retrovirus particle expression in Tera-1 and Tera-2 cells by electron microscopy revealed only a single particle with an equivocal morphology of retroviruses in a Tera-1 culture. After treatment of the cultures with iododeoxyuridine, dexamethasone, and dimethylsulfoxide for 24 hr, retrovirus particles could be easily detected in 3/4 teratocarcinoma cell lines. All other human cell cultures, including choriocarcinomas, seminomas, fibroblasts, and melanomas, etc, remained virus negative even after the induction regime. The observed particles resembled C-type retroviruses but shared a unique morphologic feature with viruses found budding from the syncytiotrophoblast of human term placentas in that their core appeared adjacent to the virus envelope without the usual intermittent space seen with C-type virus particles. After induction treatment, not only a striking increase in virus production but also an alteration in cell morphology was recognizable. In the differentiated tumor cell populations, the proportion of cells producing virus-like particles as judged by electron microscopy varied from a few in HL to over 10% in Tera-1 to almost 100% in GH cultures. While in Tera-1, GH, and HL cells, human chorionic gonadotropin (HCG) production after induction was significantly increased, this hormone was not detectable in the supernatant of Tera-2 cell cultures. Induction of enhancement of virus synthesis was thus paralleled by induction of HCG production. Reverse transcriptase activity was not clearly demonstrated in these cell lines. The teratocarcinoma viruses were not shown to be infectious. (13 Refs)

10. MORPHOLOGICAL AND MICROBIOLOGICAL SIGNS OF ENDOGENOUS C-VIRUS IN HUMAN OOCYTES.

Larsson E, Nilsson BO, Sundstrom P, Widehn S
Dept. Pathology, Biomedical Centre, Box 553, S-751 23 Uppsala, Sweden
Int J Cancer; 28(5):551-557 1981

Human oocytes in different stages of maturation were obtained by follicular aspiration from women given Clomovid and Gonadex. Particles similar to type-C virus were observed in 3 out of 16 oocytes. The particles were irregularly distributed along the oocyte membrane. They were seen both in a state of budding and lying free in the perivitelline space. Reverse transcriptase activity was detected in three out of nine samples of follicular fluid obtained from women other than those donating the oocytes. The supernatants from bat lung cells and dog thymus cells cultivated with oocytes or follicular fluids were tested for reverse transcriptase. An increased activity was observed only transiently in one case. It is assumed that these findings indicate the expression of endogenous retroviruses in human oocytes. (Author abstract) (20 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

11. HERPES SIMPLEX TYPE 1 DNA IN HUMAN BRAIN TISSUE.

Fraser NW, Lawrence WC, Wroblewska Z, Gilden DH, Koprowski H
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 78(10):6461-6465 1981

Herpes simplex virus Type 1 (HSV-1) is known to reside latently in the trigeminal ganglia of man. Reactivation of this virus causes skin lesions and may occasionally infect other tissues, including the brain. To determine whether the brain tissue of humans free of clinical signs of HSV-1 infection contains any trace of HSV-1, we examined the DNA from brain tissue by endonuclease digestion, separation of the fragments by gel electrophoresis, and hybridization with labeled HSV-1 DNA probes. Hybrid bands were detected autoradiographically in experiments using cloned and virion-purified fragments of the HSV-1 genome. HSV-1 DNA sequences were found in 6 of 11 human brain DNA samples tested. In some cases, these bands corresponded to the bands expected for the complete viral genome, whereas others contained bands representing only a part of the genome. In some cases, the terminal fragments could be found, suggesting that the DNA was in a linear, nonintegrated form. (Author abstract) (31 Refs)

12. HERPESVIRUS ATELES AND HERPESVIRUS SAIMIRI TRANSFORM MARMOSET T CELLS INTO CONTINUOUSLY PROLIFERATING CELL LINES THAT CAN MEDIATE NATURAL KILLER CELL-LIKE CYTOTOXICITY.

Johnson DR, Jondal M
Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Proc Natl Acad Sci USA; 78(10):6391-6395 1981

Herpesvirus ateles (HVA) and herpesvirus saimiri (HVS) have the capacity to transform cotton-topped marmoset T lymphocytes into continuously proliferating cell lines that retain some functions associated with cell-mediated immunity. In the present paper, we demonstrate that HVA/HVS-transformed T cell lines are cytotoxic in a short-term 51Cr release assay and that this killing resembles killing by marmoset natural killer (NK) cells. The relationship between NK cells and HVA/HVS-transformed killer cell lines is discussed in view of present knowledge of the origin and function of the NK system. It is suggested that the described cytotoxic cell lines may be useful for further defining cellular cytotoxicity with regard to cell surface recognition, regulatory events, and lytic mechanisms. (Author abstract) (37 Refs)

13. EPISOMAL AND NONEPISOMAL HERPESVIRUS DNA IN LYMPHOID TUMOR CELL LINES.

Kaschka-Dierich C, Bauer I, Fleckenstein B, Desrosiers RC
(c/o Fleckenstein), Institut fur Klinische Virologie, Loschgestrasse 7, 8520 Erlangen, W. Germany
Haematol Blood Transfus; 26:197-203 1981

Experiments were carried out on two oncogenic viruses of New World primates Herpesvirus saimiri and Herpesvirus ateles, to study the persistence of the viral DNA in host cells and the transformation of host cells by these viruses. The complete viral genomes are linear duplex DNA that contain a unique segment of L-DNA and two terminal segments of H-DNA. Transformed lymphoid tumor cells contain substantial amounts of viral L- and H-DNA, apparently as nonintegrated circular superhelical episomal DNA; they also yield a viral DNA fraction (after digestion with restriction endonucleases) that is not found in the episomal viral DNA, but the exact nature of this fraction is not yet known. The resistance of viral DNA to certain restriction endonucleases and the measured buoyant density of this DNA in cesium chloride gradients suggests that the viral DNA (both episomal and nonepisomal) is extensively methylated in nonproducer cell lines. This methylation can be reduced by conventional inhibitors of DNA methylation and by the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate. The significance of the inhibition of methylation by this tumor promoter is not known. (17 Refs)

14. ANALYSIS OF RESTRICTION ENDONUCLEASE FRAGMENTS OF INTRACELLULAR EPSTEIN-BARR VIRUS DNA AND ISOENZYMES INDICATE A COMMON ORIGIN OF THE RAJI, NC-37, AND F-265 HUMAN LYMPHOID CELL LINES.

Rymo L, Lindahl T, Povey S, Klein G
Dept. Clinical Chemistry, Univ. Gothenburg, S-413 45 Gothenburg, Sweden
Virology; 115(1):115-124 1981

Circular Epstein-Barr virus DNA molecules isolated from different virus-transformed cell lines usually show similar but distinct restriction enzyme cleavage patterns. It is shown here that EBV DNA from the cell line Raji, which is of African Burkitt lymphoma origin, has the same cleavage pattern on digestion with either EcoRI, HindIII, or BamHI as EBV DNA from two more recently established human lym phoid cell lines, NC-37 and F-265, which are presumed to be of nontumor origin. On the other hand, these three EBV DNA isolates are clearly different from DNA of the standard B95-8 strain of the virus as judged by the same criteria. A restriction enzyme cleavage map of the circular EBV DNA from Raji cells has been made to provide a basis for the comparison. The isoenzyme patterns of 14 different marker enzymes were also investigated for the Raji, NC-37, and F-265 lines and found to be closely similar. These data indicate that the NC-37 and F-265 lines are not independent isolates of human lymphoid cell lines. (Author abstract) (31 Refs)

15. SOME RECENT TRENDS IN STUDIES OF HUMAN LYMPHOID CELLS: B-CELLS, EPSTEIN-BARR VIRUS, AND TRANSFORMATION.

Zeuthen J, Klein G
Institute for Human Genetics, Bartholin Byggningen, Aarhus Univ., 8000 Aarhus C, Denmark
Haematol Blood Transfus; 26:179-190 1981

A review of recent findings in work on regulatory mechanisms involved in the selective expression of differentiated markers in human B-cell lines and the types of controls involved in the expression and function of Epstein-Barr virus (EBV)-associated markers in human cells, with special attention to the relationship between the expression of EBV functions and the expression of transformation. Because EBV is a lymphotropic virus in man, infection of lymphoid cell lines is reviewed. Chromosome studies on lymphoblastoid cell lines and B-cell lines of BL origin with regard to ploidy and karyotype abnormalities following EBV infection are discussed in detail. Studies of the immunoglobulins synthesized and the major histocompatibility antigens expressed by hybrid lymphocytes are presented. The expression of EBV, the EBV-determined nuclear antigen, and cell transformation by EBV are thoroughly reviewed. (79 Refs)

16. ANALYSIS OF THE TRANSFORMATION OF HUMAN LYMPHOCYTES BY EPSTEIN-BARR VIRUS III. INDUCTION OF EARLY EVENTS BY P3HR-1 STRAIN WITHOUT SUBSEQUENT IMMORTALIZATION.

Takada K, Osato T
Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, N15 W7, Japan
Med Microbiol Immunol (Berl); 170(1):19-26 1981

The interaction between Epstein Barr virus (EBV) derived from P3HR-1 cell line and human cord blood lymphocytes was studied by simultaneous observations of events occurring in EBV-induced transformation in individual cells. EBV derived from B95-8 cells (B95-8 EBV) was used for positive control. B95-8 EBV induced a complete series of early transformation events including nuclear antigen (EBNA) and DNA synthesis and blastogenesis, followed by immortalization of the infected lymphocytes. When the same cord preparation was exposed to P3HR-1 EBV, EBNA-positive cells were clearly identified even 12 hr after viral exposure and reached a max of 31% at 24 hr, followed by a plateau for a subsequent 24 hr. In contrast to B95-8 EBV infection, EBNA staining was weak. At 24 hr, blastogenesis was also significant while 3H-thymidine incorporation was not. In addition to weak fluorescence, brilliant EBNA staining later occurred at 48 hr and reached about 20% of the total positive cells on day 5. The EBNA-positive blast cells then became grain-positive at 36 hr and the immunofluorescent cells reached 61.1% at 120 hr. At this time, nearly 50% of the stained nuclei showed evidence of DNA synthesis. At 72 hr, all examined mitotic cells were positive for EBNA and the mitotic frequency was as high as that seen in B95-8 EBV infections. Characteristic cell aggregates were also seen. The number of infected cells decreased gradually after 1 wk and degenerated in about 2 wk. Essentially the same results were obtained, using different stocks of EBV derived from both P3HR-1 sublines A and B and different cord cell preparations. The results indicated that P3HR-1 virus does retain early transforming functions for primary human B lymphocytes, although infected cells have a short life span. (28 Refs)

17. EPSTEIN-BARR VIRUS-SPECIFIED POLYPEPTIDES IN BURKITT LYMPHOMA/SOMATIC CELL HYBRIDS (MEETING ABSTRACT).

Durnford JM, Scanlon PA, Glaser R
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Adding 5'-iododeoxyuridine (IUDR) to cultured Burkitt lymphoma/somatic cell hybrids (D98/HR-1) leads to expression of Epstein-Barr virus (EBV) early antigen (EA). When the drug is removed, the cells synthesize virus DNA, virus capsid antigen (VCA), and ultimately virus particles. The EBV-specified polypeptides present in cells before and after removal of IUDR were immunoprecipitated with serum having high antibody titers against the EBV nuclear antigen (EBNA), EA, and VCA. These polypeptides were then analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Their cellular location was determined by isolating nuclear and cytoplasmic fractions from the induced cells prior to radioimmunoprecipitation. The predominant polypetides associated with the synthesis of EA had apparent mol wt of 125 and 82 kilodaltons, respectively. The larger polypeptide was found primarily in the nucleus, whereas the smaller polypeptide was found in both nuclear and cytoplasmic fractions. Two prominent polypeptides having apparent mol wt of 141 and 133 kilodaltons were detected after the initiation of virus DNA synthesis. These appear to be the major components of VCA and may correspond to VP6 and VP7. In addition to these four prominent polypeptides, several additional polypeptides were specifically immunoprecipitated. Preliminary data suggest that the polypeptides immunoprecipitated from induced epithelial hybrid cell are very similar to those present in lymphoblasto id cells. (1 Ref)

18. ACTIVATION OF EPSTEIN-BARR VIRUS EXPRESSION IN LATENTLY INFECTED HUMAN LYMPHOBLASTOID CELLS WITH BACTERIAL FATTY ACIDS AND PROMOTORS OF PLANT AND MICROBIAL ORIGIN: A POSSIBLE CAUSE FOR BURKITT'S LYMPHOMA AND NASOPHARYNGEAL CARCINOMA (MEETING ABSTRACT).

Ito Y, Kishishita M, Yanase S, Kawanishi M, Takashima M, Ymanaka H
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

When used in combination with 12-O-tetradecanol phorbol-13-acetate (TPA) and/or croton oil, even other common fatty acids like i-butyric acid and propionic acids also exherted marked Epstein-Barr virus (EBV) inducing activity in nonproducer Raji cells. This led us to test the bacteria-produced short-chain fatty acids as EBV-inducers both with and without promotors and, found that the members of Fusobacterium, Clostridium and other species, those which produce such compounds as their metabolites, indeed play a significant role in the activation of EBV expression as detected by EBV-early (EA) and -viral capsid antigens (VCA). On the other hand, the roots of croton oil, the parent compound of TPA, was traced back to a leafy shrub, Croton tiglium, a plant native to Southeastern Asia. Incidentally, we came across a fact that the seed from which croton oil is expressed has been used as herbal drug in Southern China for over 1000 yr. This prompted us to test other analogous extracts from the Euphorbiaceae family to which C tiglium belongs. The ether extracts prepared from all these Euphorbiacea plants proved to be an efficient EBV-inducers. The Euphorbiacea plants currently used as herbal medicaments amount to more than 30 species in Southern China and as much as 90 in East Africa. We have recently observed that an indol-alkaloid produced by a variant of Streptomyces mediocidius, Teleocidin B, also can act as a powerful inducer and activator of EBV with an efficiency comparable to TPA in our producer and nonproducer test system. (1 Ref)

19. COMPARISON OF T ANTIGEN-ASSOCIATED HOST PHOSPHOPROTEINS FROM SV40-INFECTED AND -TRANSFORMED CELLS OF DIFFERENT SPECIES.

Fanning E, Burger C, Gurney EG
Fakultat fur Biologie, Universitat Konstanz, D-7750 Konstanz, W. Germany
J Gen Virol; 55(part2):367-378 1981

Simian virus 40 (SV40)-infected and -transformed cells contain, in addition to the virus-coded tumor antigens, one or more 48K to 56K host tumor antigens. At least part of this class of host proteins exists as a fast-sedimenting complex with the SV40 large T antigen. The host proteins associated with the large T antigen in SV40-transformed monkey, mouse and human cells and SV40-infected monkey cells were compared by two-dimensional gel electrophoresis and V8 partial proteolysis peptide mapping. Although these proteins differed slightly in apparent mol wt and peptide pattern, they migrated identically in isoelectric focusing gels. These results suggest that the cellular proteins associated with large T antigen in different hosts are very closely related to each other. Despite their similarities, the 55K proteins from different host cells form complexes of different stabilities with large T antigen, as judged by spontaneous dissociation of the complexes during storage, and the fractions of the 55K cellular protein and large T antigen found free and in the complexed form in each different host cell. (Author abstract) (36 Refs)

20. VIRAL GENE EXPRESSION CELLS TRANSFORMED BY SIMIAN SARCOMA VIRUS, AND INFECTIOUS PRIMATE TYPE C RETROVIRUS.

Bergholz CM
No affiliation given
Haematol Blood Transfus; 26:524-526 1981

Studies on the viral gene expression in Simian sarcoma virus (SSV)-transformed virus producing marmoset monkey cells [HF/SSV(SSAV)] and SSV-transformed nonproducer marmoset cell lines (HF/SSV-NP) are described. Using antiserum specific for SSV(SSAV: nontransforming associated virus) p30 and another specific for SSAV envelope proteins, it was demonstrated that anti-SSAV p30 precipitates predominantly polypeptides of approx 30,000 and 60,000-62,000 daltons and, in addition, polypeptides of approx 72,000 and 52,000 daltons. Results of pulse-chase experiments indicated that the 60,000 dalton protein (pr60gag) is processed to yield p30, the major viral core protein. Using antiserum specific for gp70 and p15E/p12E, large amounts of 82,000 dalton polypeptide were precipitated; results of pulse-chase experiments indicated that it is an envelope precursor protein processed to yield p15E and p12E. Two virus-specific phosphoproteins, the pr60gag and p12 were revealed by electrophoresis. No phosphorylated proteins were precipitated by antiserum specific for SSAV envelope proteins. IgG was phosphorylated in extracts of both HF/SSV(SSAV) and HF/SSAV cells, but not in extracts of HF/SSV-NP cells. Expression of SSAV-related sequences by the SSV provirus was investigated by reacting an SSAV circular DNA with increasing concentrations of RNA extracted from two HF/SSV-NP cell lines. The results indicated that SSAV-related sequences were transcribed but represented a smaller proportion of the total cell RNA relative to virus producing cells. Comparison of max levels of hybridization indicated that less of the SSAV genome is represented in the SSV transcripts relative to RNA in SSAV-infected cells. The failure to detect virus-specific proteins in five HF/SSV-NP cells lines shown to contain SSAV-related cytoplasmic RNA suggested that translation of this RNA may be restricted. (1 Ref)

VIRUS REPLICATION AND EXPRESSION

21. REPAIR OF PSORALEN-TREATED DNA BY GENETIC RECOMBINATION IN HUMAN CELLS INFECTED WITH HERPES SIMPLEX VIRUS.

Hall JD, Scherer K
Dept. Cellular and Developmental Biology, Univ. Arizona, Tucson, AZ, 85721
Cancer Res; 41(12):5033-5038 1981

Herpes simplex virus type 1 was treated with 4,5',8-trimethylpsoralen (psoralen) plus near-UV light in order to produce lesions (monoadducts and DNA cross-links) in the viral DNA. Human fibroblasts were infected by damaged virus under conditions in which either a single virus particle or several particles entered a given cell, and the fraction of virus-producing cells was determined. This fraction was significantly greater for multiply infected cells than for singly infected cells, indicating that the psoralen lesions are repaired more efficiently in the presence of homologous, damaged DNA (multiplicity reactivation). Evidence is presented that herpes simplex virus may code for functions which participate in its own repair, both during multiplicity reactivation and during repair which occurs in singly infected cells: (a) host cells deficient in repair of lesions induced by psoralen (xeroderma pigmentosum) or the DNA cross-linking agent mitomycin C (Fanconi's anemia) exhibited normal levels of multiplicity reactivation of psoralen-treated herpes virus; (b) while xeroderma pigmentosum cells have been previously shown to be deficient in repair of psoralen-treated adenovirus under conditions of single infection, herpes virus is repaired at near normal levels in these same cells. Recombination levels between genetically marked pairs of herpes viruses were found to increase after treatment of the parental viruses with psoralen, suggesting that psoralen damage stimulates genetic recombination. This stimulation provides convincing evidence for a repair pathway in which genetic recombination between damaged viral genomes can lead to the production of viable virus. (Author abstract) (28 Refs)

22. EPSTEIN-BARR VIRUS-INDUCED PROTEINS. IV. CHARACTERIZATION OF AN EBV-ASSOCIATED PHOSPHOPOLYPEPTIDE.

Mueller-Lantzsch N, Yamamoto N
Schweizerisches Serum und Impfinstitut, Bern, Switzerland
J Gen Virol; 55(part2):333-341 1981

Cells of the Epstein-Barr virus (EBV) non-producing lines NC37 and Raji were induced by the tumor promoter TPA and were labelled with 32P. The analysis by immunoprecipitation with human VCA+EA+ sera revealed that a major phosphopolypeptide with a mol wt of 58,000 was specifically precipitated. In addition, a phosphopolypeptide of the same size was the dominant phosphopolypeptide detected in EBV-producing B95-8 and P3HR-1 cells as well as in P3HR-1-superinfected NC37 cells. This phosphopolypeptide seemed to be EBV-specific, because it was not detectable in TPA-treated, but EBV genome-negative, Ramos and BJAB cells. Synthesis of this phosphopolypeptide was inhibited in TPA-treated NC37 cells by treatment with Ara-C. VCA+EA+ sera were found to be more immunoreactive with this phosphopolypeptide than VCA+EA- or EBNA+ sera. Based on these results this phosphopolypeptide may have some immunological relatedness to the EBV-specific early antigen (EA) complex defined by immunofluorescence. (Author abstract) (29 Refs)

23. CONTROL OF ADENOVIRUS EARLY GENE EXPRESSION: ACCUMULATION OF VIRAL MRNA AFTER INFECTION OF TRANSFORMED CELLS.

Persson H, Katze MG, Philipson L
Dept. Microbiology, Biomedical Center, S-751 23 Uppsala, Sweden
J Virol; 40(2):358-366 1981

We studied the accumulation of viral mRNA in the presence of inhibitors of protein synthesis in an adenovirus Type 5-transformed cell line (line 293 cells). An analysis of the endogenous viral mRNA's and proteins revealed that only early regions 1A and 1B were expressed in uninfected 293 cells. However, viral mRNA's from early regions 2, 3, and 4, as well as mRNA's from early regions 1A and 1B, accumulated in 293 cells after infection with adenovirus Type 2. Cells treated with anisomycin before infection showed a drastic enhancement of mRNA from early region 4 compared with drug-free controls. This increase in viral mRNA was detected by using filter hybridization, S1 endonuclease mapping, and in vitro translation. The rate of transcription of early region 4 nuclear RNA also increased significantly in the presence of anisomycin. In contrast to the results with early region 4, the levels of cytoplasmic mRNA's from early regions 2 and 3 did not increase in cells treated with inhibitors. These results suggested that multiple virus encoded controls operate on the early regions of the adenovirus genome. (Author abstract) (31 Refs)

24. LATE NONSTRUCTURAL 100,000-AND 33,000-DALTON PROTEINS OF ADENOVIRUS TYPE 2: I. SUBCELLULAR LOCALIZATION DURING THE COURSE OF INFECTION.

Gambke C, Deppert W
Friedrich Miescher Inst., CH-4002 Basel, Switzerland
J Virol; 40(2):585-593 1981

We analyzed the subcellular locations of the late adenovirus Type 2 nonstructural 100,000-dalton (100K) and 33K proteins in adenovirus Type 2-infected HeLa cells both by biochemical cell fractionation and by immunofluorescence microscopy, using specific antisera against purified sodium dodecyl sulfate-denatured 100K and 33K polypeptides. Both methods showed that the 100K protein was present in the cytoplasm as well as in the nuclei of infected cells and that it accumulated in the nuclei during the course of infection. Phosphorylated 100K protein also was found both in the cytoplasm and in nuclei. However, the nuclear 100K protein pool was phosphorylated to a higher degree than the cytoplasmic pool. In all experiments the 33K protein, which also is a phosphoprotein, was present exclusively in the nuclei of infected cells. The 100K and 33K proteins were associated with different nuclear substructures; this was demonstrated serologically by an analysis of infected cells in which double color immunofluorescence microscopy was used. In these experiments antibodies against the 100K protein decorated different nuclear structures than antibodies against the 33K protein. (Author abstract) (30 Refs)

25. KINETICS OF INHIBITION OF PAPOVAVIRUS DNA SYNTHESIS BY SUPERINFECTION WITH ADENOVIRUS 2 AND NON-DEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Patch CT, Howley PM, Hauser J, Levine AS
Section Infectious Disease, Pediatric Oncology Branch, NCI, NIH, Bethesda, MD, 20205
J Gen Virol; 55(part2):355-365 1981

Simian Virus 40 (SV40) DNA synthesis is inhibited in monkey cells by superinfection with adenovirus 2 (Ad2) and various non-defective Ad2-SV40 hybrid viruses. Similarly, BKV (a human papovavirus) DNA synthesis is inhibited in human cells by superinfection with Ad2. Kinetic studies indicate that inhibition begins during the early phase of the Ad2 lytic cycle. Superinfection with Ad2 does not significantly alter the formation of SV40 T antigen. Superinfection with Ad2 late in the SV40 lytic cycle is less efficient in the inhibition of SV40 DNA synthesis, and the onset of Ad2 DNA synthesis is delayed, compared to superinfection early in the SV40 lytic cycle. These findings suggest that the Ad2 and SV40 genomes may compete to bind an early Ad2 protein which is essential for Ad2 replication, but which blocks SV40 replication. (Author abstract) (28 Refs)

26. CELL SURFACE T ANTIGEN IN CELLS INFECTED WITH SIMIAN VIRUS 40 OR AN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID, AD2+D2.

Ismail A, Baumann EA, Hand R
McGill Cancer Centre, Dept. Medicine, McGill Univ., Montreal, Quebec H3G 1Y6, Canada
J Virol; 40(2):615-619 1981

Cell surface T antigen, detected by a radioimmune assay that uses 125I-labeled Staphylococcus aureus protein A and antibodies against either authentic T antigen or D2 hybrid T antigen, was found in simian virus 40-transformed and -infected cells and in cells infected with an adenovirus-simian virus 40 hybrid, Ad2+D2. In simian virus 40 lytic infection, the surface T antigen appeared at the same time as the nuclear T antigen. (Author abstract) (22 Refs)

27. MODULATION IN EXPRESSION OF HLA ANTIGENS IN CULTURED CELLS. EFFECT ON DETERMINING THE INCORPORATION HOST CELL MEMBRANE ANTIGENS IN VIRAL ENVELOPES (MEETING ABSTRACT).

Azocar J, Yunis E, Essex M
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

Cultured human lymphoid cell lines undergo modulation in the expression of HLA antigens. This modulation is characterized by a gradual loss in HLA expression at the cell membrane as determined by decreased reactivity with anti-HLA alloantisera in the complement dependent microcytotoxicity assay; and by a decreased cell reactivity with monoclonal anti-HLA antibodies using radioimmunoassay techniques. As determined by these two methods, the gradual loss in HLA expression seems to be directly related to cell density conditions in the culture system; ie, those cells cultured at high cell densities (HD) undergo a more drastic modulation in HLA expression than those cultured at low density (LD). The incorporation of cell HLA antigens in the envelope of oncornaviruses seems to be influenced by the degree of HLA modulation in the infected cell at the time of virus budding. This is indicated by the fact that feline leukemia virus (FeLV) produced by infected human lymphoid cells is neutralized by anti-HLA alloantibody against the HLA determinants present in the producer cells, in a complement dependent reaction However, the degree of virus neutralization is influenced by the density conditions of the virus producer cells, in such a way that virus produced by infected cells cultured at HD are less sensitive to neutralization by anti-HLA alloantisera, as compared to virus produced by infected cells cultured at LD. Those results suggest that incorporation of HLA antigens in the envelope of budding viruses is a random phenomenon, determined by the expression of HLA antigens at the cell membrane at the time of virus budding rather than by the product of a selective viral mechanism. Because cytotoxic T lymphocytes (CTL) recognize major histocompatibility antigens during the killing of virus infected and/or tumor cells, it is possible that virus infected and tumor cells undergoing HLA modultion may be resistant to CTL killing. (4 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

28. NUCLEOTIDE SEQUENCES OF THE JOINT BETWEEN THE L AND S SEGMENTS OF HERPES SIMPLEX VIRUS TYPES 1 AND 2.

Davison AJ, Wilkie NM
Medical Res. Council Virology Unit, Univ. Glasgow, Church St., Glasgow G11 5JR, England
J Gen Virol; 55(part2):315-331 1981

The a sequence of herpes simplex virus (HSV) is present as a direct repeat at the genomic termini and also in inverted orientation at the joint between the L and S segments. DNA sequences have been determined for the joint regions of the genomes of HSV-1 and HSV-2, and relative to these sequences the genomic termini are in both cases located close to a short direct repeat of 17 to 21 base pairs (bp) at the b-a and a-c junctions. The HSV-1 joint region contains three separate tandem direct reiterations of short sequences, (12, 16 and 17 bp in strain 17) and we conclude that size heterogeneity in the a and c sequences is due to variable copy numbers of these repeated units. It is likely that a considerable part of the HSV-1 joint region does not code for polypeptide. (Author abstract) (54 Refs)

29. EPSTEIN-BARR VIRUS DNA: X. DIRECT REPEAT WITHIN THE INTERNAL DIRECT REPEAT OF EPSTEIN-BARR VIRUS DNA.

Cheung A, Kieff E
Section Infectious Disease, Dept. Medicine, Kovler Viral Oncology Lab., Univ. Chicago, Chicago, IL, 60637
J Virol; 40(2):501-507 1981

The 3,360-base-pair internal direct repeat (IR) in Epstein-Barr virus DNA separates the short and long unique DNA domains. IR has a single BamHI site. The juncture between the short unique domain and IR has been mapped by restriction endonucleases and is less than 2,600 nucleotides before the BamHI site in IR. The junction between IR and the long unique domain has been sequenced and is approx 650 nucleotides after the BamHI site in IR. Thus, relative to the start of IR at the juncture with the short unique domain, the last repeat is at least 90 base pairs short of being complete. There is homology between the 250-nucleotide fragments to the left and the right of the unique BamHI site in IR. A 35-base-pair sequence of the left fragment is directly repeated within the right fragment, once fully and once partially. The implications of these findings are discussed. (Author abstract) (27 Refs)

30. MECHANISM OF ACTIVATION OF EARLY VIRAL TRANSCRIPTION BY THE ADENOVIRUS E1A GENE PRODUCT.

Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 26(2,part2):213-220 1981

Results obtained with certain adenovirus host range mutants (dl312 and hr1) have demonstrated that a functional viral E1A gene is required for the accumulation of early viral mRNA. In this report, it is demonstrated that the failure to accumulate early viral mRNA in E1A mutant-infected cells is due to a lack of transcription of the appropriate transcription units. The E1A gene product appears to enhance transcription of the early transcription units since there is not an absolute requirement for its function. At low multiplicities of infection, transcription from the early transcription units can be detected but at a later time. By increasing the multiplicity of infection, this slow activation of early transcription can be enhanced, even though at this multiplicity all input viruses are still mutant. It was also found that early transcription could be detected in mutant-infected cells if the virus was added to cells in which protein synthesis was inhibited prior to infection. Thus inhibition of cellular protein synthesis can mimic the function of the E1A gene. It is proposed that the role of the E1A gene product in the activation of early viral transcription is to inactivate a cellular factor that prevents transcription from the other early viral promoters. (Author abstract) (48 Refs)

31. EXPRESSION OF EARLY ADENOVIRUS GENES REQUIRES A VIRAL ENCODED ACIDIC POLYPEPTIDE.

Ricciardi RP, Jones RL, Cepko CL, Sharp PA, Roberts BE
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 78(10):6121-6125 1981

Host-range mutants of adenovirus 5 that contain a defect in region E1A (0-4.5 units) fail to replicate in HeLa cells and to transform rodent cells. In HeLa cells, these mutants synthesize only the two RNAs from E1A that share the same 5' and 3' termini but differ in length by the amount of internal sequence removed by splicing. RNA from wild-type virus, selected by hybridization to DNA from region E1A, translates into polypeptides of Mr 51,000 and 48,000 that are highly acidic in isoelectric focusing gels. These acidic Mr 51,000 and Mr 48,000 polypeptides are encoded by the longer and shorter E1A RNAs, respectively. Two of the host-range mutants, H5hr1 and H5hr2, fail to synthesize the Mr 51,000 polypeptide but do produce the Mr 48,000 polypeptide and a novel polypeptide thought to be a truncated portion of the Mr 51,000 polypeptide. H5hr1 and H5hr2 are hypothesized to have termination codons in sequences found only in RNA encoding the Mr 51,000 polypeptide. This prediction is verified for H5hr1 by DNA sequence analysis. The other three host-range mutants (H5hr3-5) synthesize both acidic polypeptides and are predicted to be missense. These results strongly imply that the Mr 51,000 polypeptide, alone or in combination with the Mr 48,000 polypeptide, is needed to regulate expression of adjacent viral genes during the early phase of adenovirus infection. (Author abstract) (34 Refs)

32. MAPPING OF RNAS TRANSCRIBED FROM ADENOVIRUS TYPE 12 EARLY AND VA RNA REGIONS.

Saito I, Sato JI, Handa H, Shiroki K, Shimojo H
(c/o Shimojo) Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108, Japan
Virology; 114(2):379-398 1981

We have defined the sizes and map positions of adenovirus type 12 (Ad12) cytoplasmic RNAs produced during the early and intermediate phases of infection using the nuclease S1-gel technique. S1-protected [32P]DNAs were analyzed in conventional neutral and alkaline agarose gels as well as in a two-dimensional agarose gel system. In Ad12 early regions 1A, 1B, 2, 3, and 4, were identified four, three, one, five, and five mRNA species, respectively. These mRNAs formed family structures, commonly shared a limited variety of 3' and/or 5' end positions and multiple splicing patterns. Most mRNAs showed all possible combinations of terminal positions and splicing patterns. In spite of these complex features, a remarkable similarity was observed between Ad12 and Ad2 mRNA structures in each early region. However, several differences were observed in these early regions, especially in early region 3. Only a single species of Ad12 VA RNA was detected near 30 map units, as with Ad2 VA RNAI. (Author abstract) (25 Refs)

33. LOCALIZATION OF HEXONE-ENCODING GENE IN GENOME OF SIMIAN ADENOVIRUSES.

Vilnis AE, Loparev VN, Zavizion BA, Tarasishin LA, Khil'ko SN, Naroditskii BS, G rodnitskaia NA, Vikhnovich EM, Manykin AA
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Vestn Akad Med Nauk SSSR; (9):88-94 1981

Comparative analysis of oligopeptide and nucleotide sequences of human adenoviruses Ad2 and Ad6 and simian adenovirus SA7 (C-8) showed that hexone-encoding gene is localized in the region of 50-60-unit of genome. (23 Refs) (In RUS)

34. GENOMIC ARRANGEMENT OF AN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID VIRUS, AD2+ND4DEL.

Westphal H
Lab. Molcular Genetics, Nat. Inst. Child Health and Human Development, Bethesda, MD, 20205
J Virol; 40(2):526-532 1981

Ad2+ND4del is an adenovirus Type 2-simian virus 40 hybrid virus nondefective for growth in human cells. The virus was first observed when stocks of Ad2+ND4, a hybrid isolated from primary monkey kidney cells, were propagated in human cells. This paper describes the DNA sequence at two sites of DNA recombination, the site of the left adenovirus Type 2-simian virus 40 junction and the site of a deletion of internal simian virus 40 sequences. Since the deletion was observed when the virus was switched from monkey to human cells, an analysis of gene expression in the region of DNA rearrangement may prove useful for the elucidation of molecular events that accompany virus growth in different hosts. (Author abstract) (34 Refs)

35. EXPRESSION OF ADENOVIRUS TYPE 2 LATE GENES IN HELA CELLS INFECTED WITH ADENOVIRUS TYPE 2 OR ADENOVIRUS TYPE 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Lawrence CB
Dept. Cell Biology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
J Virol; 40(2):610-614 1981

The relative levels of expression of the five 3'-coterminal mRNA families encoded in the 16.4 to 99 map unit transcription unit of adenovirus Type 2 (Ad2) are determined in part by the frequency of utilization of five possible polyadenylation sites. The possibility that polyadenylation frequencies at these sites may be regulated was tested by examining the expression of the fiber (polypeptide IV) gene in cells infected with nondefective (ND) Ad2-simian virus 40 hybrid viruses which express a sixth late mRNA family. Both the relative rate of fiber protein synthesis and the relative abundance of fiber mRNA were normal in cells infected with the hybrid viruses Ad2+ND1, Ad2+ND2, or Ad2+ND4. (Author abstract) (23 Refs)

36. USE OF WHOLE-CELL FIXATION TO VISUALIZE REPLICATING AND MATURING SIMIAN VIRUS 40: IDENTIFICATION OF NEW VIRAL GENE PRODUCT.

Jackson V, Chalkley R
Dept. Biochemistry, Sch. Medicine, Univ. Iowa, Iowa City, IA, 52242
Proc Natl Acad Sci USA; 78(10):6081-6085 1981

Formaldehyde fixation of simian virus 40 (SV40)-infected CV-1 cells at appropriate times after infection permits us to isolate crosslinked complexes of SV40 minichromosomes during the t ime of DNA replication and during packaging with viral proteins. Such crosslinked complexes can be separated on the basis of density on CsCl/guanidine.HCl density gradients. During the course of these studies we observed the presence of a low mol wt protein in a region of the gradient much enriched with viral nucleoproteins. This protein is present only in infected cells and has a mol wt and amino acid composition consistent with it being the product of the so-called SV40 agnogene. (Author abstract) (21 Refs)

37. PREFERENTIAL ASSOCIATION OF URACIL-DNA GLYCOSYLASE ACTIVITY WITH REPLICATING SV40 MINICHROMOSOMES.

Krokan H
Inst. Medical Biology, Univ. Tromso, 9001 Tromso, Norway
FEBS Lett; 133(1):89-91 1981

The preferential association of a major DNA repair enzyme, uracil-DNA glycosylase, with replicating SV40 minichromosomes in investigated. A nuclear extract containing SV40 minichromosomes, but free of cellular DNA and mitochondria was centrifuged to separate replicating and mature minichromosomes. Uracil-DNA glycosylase was tested by collecting fractions from the nuclear extract and incubating with an assay buffer and d3H uracil monophosphate (dUMP) containing DNA. The release of acid or ethanol soluble radioactivity was monitored. Cytochrome c oxidase was determined in aliquots of 100 ul from extracts or gradient fractions. To label both replicating and mature SV40 chromatin, SV40 infected CV-1 cells were incubated with 14C thymidine. Nuclear extracts were prepared as above. Uracil-DNA glycosylase activity was measured in each fraction. Results showed that uracil-DNA glycosylase cosediments with replicating chromatin; a smaller fraction cosedimented with mature chromatin. Thin layer chromatography of the ethanol soluble radioactivity released showed 90% comigrated with uracil. No cytochrome c oxidase activity cosedimented with SV40 minichromosomes. Apparently cosedimentation of uracil-DNA glycosylase with replicating chromatin is not due to contamination by mitochondria. The results suggest that uracil-DNA glycosylase is preferentially associated with replicating SV40 minichromosomes. This may indicate that misincorporation of dUMP is a more frequent event than cytosine deamination. (24 Refs)

38. THE CARCINOGEN N-ACETOXY-ACETYLAMINOFLUORENE REACTS PREFERENTIALLY WITH A CONTROL REGION OF THE INTRACELLULAR SIMIAN VIRUS 40 CHROMOSOME (MEETING ABSTRACT).

Beard P, Kaneko M, Cerutti P
No affiliation given
Experientia; 37(6):638 1981

We have investigated the binding of the ultimate carcinogen N-acetoxy-acetylaminofluorene (AAAF) to specific regions of the SV40 chromosome in situ in the intact infected cell. SV40-infected cells late in the lytic cycle were incubated with 3H-AAAF. SV40 DNA was extracted, digested with restriction enzymes Hae III and Kpn I and radioactivity in each DNA fragment determined. The results indicated that a stretch of DNA near the origin of replication of the intracellular SV40 chromosome was more susceptible to attack by AAAF than the rest of the SV40 genome. When naked DNA was labeled with 3H-AAAF in vitro no hyperreactive region was seen. The hyperreactive region may represent a stretch of DNA which is nucleosome-free or has another unusual chromosomal structure. (no Refs)

39. STIMULATION OF POLYOMA DNA REPLICATION IN ISOLATED NUCLEOPROTEIN COMPLEXES BY FACTORS FROM DROSOPHILA EMBRYOS.

Mastromei G, Eliasson R, Reichard P
Instituto di Genetica, Universita di Pavia, 27100 Pavia, Italy
J Mol Biol; 151(4):627-643 1981

Nucleoprotein complexes containing both Form 1 and replicative intermediates of polyoma DNA prepared from nuclei of virus-infected mouse fibroblasts retain a limited ability to elongate progeny strands of the replicative intermediates. Compared to isolated nuclei, both the rate and the extent of strand elongation is greatly decreased. The isolated complexes synthesize initiator RNA and start new Okazaki fragments, but are deficient in the joining of these fragments. Addition of small amounts of an extract from 16 hr old Drosophila embryos corrects the deficiencies. The stimulatory activity of the extract can be partially purified and has been separated into two fractions by chromatography on Sepharose 6B. With immunological techniques we demonstrate that the mouse DNA polymerase-alpha, tightly bound to the complexes, is responsible for DNA strand elongation. The Drosophila alpha-polymerase present in one of the two fractions purified on Sepharose 6B cannot substitute for the mouse enzyme. The stimulatory activity of the Drosophila fractions is thus not due to alpha-polymerase. (Author abstract) (21 Refs)

40. CHARACTERIZATION BY NUCLEIC ACID HYBRIDIZATION OF HTLV, A NOVEL RETROVIRUS FROM HUMAN NEOPLASTIC T-LYMPHOCYTES.

Reitz MS, Poiesz BJ, Ruscetti FW, Gallo RC
Natl. Cancer Inst., Bethesda, MD, 20014
Haematol Blood Transfus; 26:515-516 1981

Cyclic DNA (cDNA) and 70S RNA were prepared from the novel human neoplastic T-lymphocyte retrovirus HTLV. These probes were used to determine (1) degree of relatedness to other viruses, (2) whether or not HTLV is endogenous, and (3) whether related sequences can be found in other human tissues. HTLV cDNA hybridized 90% to its own 70S RNA; it did not hybridize significantly to a variety of retroviruses including murine and feline leukemia and sarcoma viruses, baboon endogenous virus, squirrel monkey retrovirus, Mason-Pfizer virus, bovine leukemia virus, RD114 endogenous cat virus, murine mammary tumor virus, and avian myeloblastosis virus. Low (5-10%) levels of hybridization were achieved with 70S from woolly monkey virus and gibbon ape leukemia virus. No HTLV hybridization was obtained with DNA or RNA from normal h uman peripheral blood T-lymphocytes, with DNA from non- neoplastic autopsy tissues or peripheral blood samples from patients with acute myelogenous leukemia, chronic myelogenous leukemia, or chronic lymphocytic leukemia. DNA from 1/3 acute lymphocytic leukemias (ALL) and 1/2 Sezary syndrome peripheral blood samples hybridized a significant 20-25% of HTLV cDNA. The positive ALL was T-cell. HTLV appears to be a novel retrovirus isolate not endogenous to humans. Results suggest that it is associated with T-cell lymphomas and leukemias of mature cell type. (1 Ref)

IMMUNOLOGICAL STUDIES

41. HERPES SIMPLEX VIRUS TYPE 1 AND 2 INTRACELLULAR P40: TYPE-SPECIFIC AND CROSS-REACTIVE ANTIGENIC DETERMINANTS ON PEPTIDES GENERATED BY PARTIAL PROTEOLYSIS.

Heilman CJ, Zweig M, Hampar B
Lab. Molecular Virology, Carcinogenesis Intramural Program, NCI, Frederick, MD, 21701
J Virol; 40(2):508-515 1981

Intracellular p40 is a class of protein ranging in mol wt from 39,000 to 45,000 that is immunoprecipitated from herpes simplex virus type 1 (HSV-1)- and HSV-2-infected cell extracts by mouse monoclonal antibodies or guinea pig antisera against HSV-1 and HSV-2 nucleocapsid p40. Analysis by a two-dimensional gel system showed that HSV-1 and HSV-2 intracellular p40 each consisted of three major components. However, these HSV-1 and HSV-2 proteins differed in charge and size. Analysis of Staphylococcus aureus V8 protease partial digests by two-dimensional gel electrophoresis indicated that none of the peptides of HSV-1 and HSV-2 intracellular p40 were identical. Immunoprecipitation of the partial digest products of intracellular p40-1 and p40-2 with homologous and heterologous guinea pig antisera resulted in the precipitation of various combinations of peptides indicating the presence of either type-specific or cross-reactive antigenic determinants. (Author abstract) (17 Refs)

42. A GEOGRAPHICAL STUDY OF ANTIBODIES TO MEMBRANE ANTIGENS OF HSV-2-INFECTED CELLS AND HSV-2-SPECIFIC ANTIBODIES IN PATIENTS WITH CERVICAL CANCER.

Mendis LN, Best JM, Senarath L, Chiphangwi J, Vestergaard BF, Banatvala JE
Dept. Microbiology, Faculty of Medicine, Post Office Box 271, Kynsey Road, Colombo 8, Sri Lanka
Int J Cancer; 28(5):535-542 1981

Sera were obtained from patients with squamous carcinoma of the cervix from Great Britain (29), Sri Lanka (32), Malawi (27) and Sudan (27), and from controls from all countries except Sudan. Controls were matched for ethnic origin, age and social class. Sera were tested by indirect immunofluorescence (IF) for IgG and IgA antibodies to membrane antigens (MA) and IgA antibodies to VCA of HSV-2 infected cells. Compared with controls, IgA antibodies to MA (IgA anti-MA) were detected more frequently and at higher titers in all groups of patients. However, there was no significant difference in prevalence of these antibodies at titers greater than or equal to 1:4 between Malawian patients and controls, although a significantly higher proportion of patients had IgA anti-MA titers of greater than or equal to 1:16. In contrast, IgA anti-VCA did not distinguish patients from controls. More than 90% of both patients and controls from all countries had IgG antibodies to MA (IgA anti-MA). Malawian patients had a significantly higher geometric mean titer (GMT) of IgG anti-MA than controls and both patients and controls had significantly higher GMTs than their counterparts from other countries. The variation between herpes IgG anti-MA titers in subjects from different countries did not reflect differences in serum Ig levels and similar variations in titer were not seen in rubella and measles HAI titers. Among the patients there was a geographical variation in the prevalence of HSV-2 specific antibodies detected by ELISA, which varied from 52% among British and Sudanese patients to 73% among Malawian patients. Even when adjustment was made for possible false negative results, there were between 10 and 31% patients without HSV-2-specific antibodies, although only 2 of 103 (1.9%) patients had neither HSV-1 nor HSV-2 antibodies. The association of HSV-2 with cervical carcinoma appeared to vary with age. (Author abstract) (52 Refs)

43. STIMULATION WITH AUTOLOGOUS LYMPHOBLASTOID CELL LINES: LYSIS OF EPSTEIN-BARR VIRUS-POSITIVE AND -NEGATIVE CELL LINES BY TWO PHENOTYPICALLY DISTINGUISHABLE EFFECTOR CELL POPULATIONS.

Zarling JM, Dierckins MS, Sevenich EA, Clouse KA
Immunobiology Res. Center, Univ. Minnesota, Minneapolis, MN, 55455
J Immunol; 127(5):2118-2123 1981

Human lymphocytes, stimulated in vitro for 6 days with x-irradiated or glutaraldehyde-treated autologous Epstein-Barr (EB) virus-transformed lymphoblastoid cell lines (LCL), are cytotoxic for autologous and allogeneic EB+ LCLs as well as for several EB- cell lines that are also susceptible to lysis by interferon-activated natural killer (NK) cells. To determine whether the apparent nonspecific lysis mediated by LCL-stimulated cells is due to a mixture of effector cells directed against different target cells, advantage was taken of our recent finding that monoclonal antibody OKT8 reacts with human cytotoxic T lymphocytes but not with NK cells or NK-like cells generated in mixed WBC cultures. The depletion of OKT8+ cells from LCL-stimulated cultures by treatment with OKT8 and complement abolished or markedly depleted cytotoxicity against all EB+ target cells tested, whereas cytotoxicity against EB-, NK-sensitive cell lines including K562, MOLT-4 and HSB-2 was not or only minimally reduced. These results indicate that stimulation with autologous LCL results in the generation of OKT8+ cytotoxic T lymphocytes that lyse EB virus-transformed LCL and OKT8-NK-like cells that lyse EB-, NK-sensitive cells. (Author abstract) (36 Refs)

44. DYNAMICS OF EPSTEIN-BARR VIRUS ANTIBODIES IN HODGKIN'S DISEASE.

Vanecek K, Holy J, Hrodek O, Hynieova H, Ptrtylova K, Srajer J

Ustav vyzkumu a vyvoje ditete, Fakulta detskeho lekarstvi KU, V uvalu 84, 150 06 Prague 5-Motol, Czechoslovakia

Cesk Pediatr; 36(8):449-452 1981

The dynamics of antibodies to Epstein-Barr Virus capsid antigen (VCA/EBV) was studied in 38 children (26 boys and 12 girls) with Hodgkin's disease (HD). The course of the disease was protracted with remissions and recurrences in 16 cases (Group A), short, with death in a short time in 5 (Group B), and 17 other patients (Group C) were in remission without recurrence for 3-5 yr after treatment. The treatment consisted of radiotherapy followed by single-agent or polychemotherapy with cyclophosphamide, vinblastine, prednisone, and procarbazine. The antibody titer correlated with the severity and course of the disease, dropping rapidly from a very low level in Group B, and rising from higher initial levels in Group A and especially C. The antibody titers were not affected by the treatment. (7 Refs) (In CZE)

45. MONOCLONAL ANTIBODY AGAINST A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN.

Wiels J, Fellous M, Tursz T

Laboratoire d'Immunologie Clinique, Institut Gustave-Roussy, 94800 Villejuif, France

Proc Natl Acad Sci USA; 78(10):6485-6488 1981

A monoclonal antibody, referred to as 38.13, was obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma containing Epstein-Barr virus genome but lacking HLA-A, -B, and -C and beta2-microglobulin molecules at the cell surface). 38.13 antibody was demonstrated to be a rat IgM. By complement-dependent microcytotoxicity and indirect immunofluorescence assays, 38.13 antibody was shown to react specifically with cells derived from Burkitt tumors, including both Epstein-Barr virus genome-carrying and Epstein-Barr virus-negative Burkitt lymphoma. By contrast, Epstein-Barr virus-containing lymphoblastoid cell lines derived from normal B lymphocytes were not recognized by 38.13 antibody. Fresh malignant cells from patients affected with various lymphoproliferative disorders were negative, except 4/8 having abdominal Burkitt-like lymphomas. Normal lymphocytes from peripheral blood, spleen, lymph node, tonsil, and bone marrow and mitogen (phytohemagglutinin, pokeweed mitogen, and concanavalin A)-activated blasts were also negative. Thus, 38.13 antibody apparently recognized a Burkitt-associated antigen that is not related to Epstein-Barr virus. The pattern of reactivity of 38.13 antibody with various Burkitt lymphoma cells appeared quite heterogenous and some Burkitt cells were consistently negative. 38.13 antibody thus defines a subset of Burkitt lymphomas. (Author abstract) (18 Refs)

46. INDUCTION OF MARMOSET CELLULAR CYTOTOXICITY TO AUTOLOGOUS EBV-TRANSFORMED LYMPHOBLASTOID CELL LINES (MEETING ABSTRACT).

Abb J, Deinhardt F

No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Marmosets have proven particularly useful as animal models for viral oncogenesis. Experimental infection of these small New World primate with Epstein-Barr virus (EBV) leads to the development of lymphomas or lymphocytic leukemias. Transformation of marmoset peripheral blood lymphocytes (PBL) with EBV in vitro allows the establishment of permanent lymphoblastoid cell lines (LCL) with B-cell characteristics. Studies on the immune response of marmosets in vitro to EBV-associated antigens expressed on autologous LCL have shown that cell-mediated cytotoxicity could not be induced in conventional mixed lymphocyte-LCL cultures (MLLC). Cytotoxic effector cells to autologous marmoset EBV-LCL, however, were induced by the addition of third party allogeneic or xenogeneic lymphocytes to marmoset PBL and autologous EBV-LCL in vitro. The induced cytotoxic lymphocytes had the morphological and functional characteristics of natural killer (NK) cells: Marmoset effector cells were nonadherent and possessed receptors for Fc-IgG; effector cells showed no restriction for antigens of the major histocompatibility complex (MHC) or EBV-genome positive target cells; effector cell activity appeared to be regulated by the endogenous production of interferon (IF) in third party MLLC. Further evidence for the regulatory role of IF was provided by the observation that lymphocyte cytotoxicity to autologous EBV-LCL could also be induced by incubation of marmoset PBL with partially purified human WBC IF or with IF inducers (lectin mitogens, poly I:C). Addition of antiserum to human WBC IF to third party MLLC inhibited the induction of cell-mediated cytotoxicity to autologous marmoset EBV-LCL. (no Refs)

47. LIVER CELL DYSPLASIA IN ASSOCIATION WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS AND HEPATITIS B SURFACE ANTIGEN IN HONG KONG.

Ho JC, Wu PC, Mak TK

Dept. Pathology, Univ. Hong Kong, Hong Kong, China

Int J Cancer; 28(5):571-574 1981

Liver-cell dysplasia was identified in 60% of 558 cases of cirrhosis with and without hepatocellular carcinoma (HCC) in Chinese coming to necropsy in Hong Kong from 1963 to 1978. A significant correlation was found between liver-cell dysplasia and the identification of hepatitis B surface antigen (HBsAg) in the livers, suggesting that dysplasia may be causally related to hepatitis B virus (HBV). Applying Bayes' theorem to our series of male deaths, we calculated that for Chinese male non-cirrhotics showing liver-cell dysplasia at necropsy, compared with male non-cirrhotics showing no liver-cell dysplasia, the approximate risk factor for HCC is 13:1, whereas for male cirrhotics with liver-cell dysplasia, compared with male cirrhotics without liver cell dysplasia, the risk factor for HCC is approx 2:1. In the presence of dysplasia, the risk for HCC is increased two-fold in males who are also HBsAg-positive. Thus, the presence of liver-cell dysplasia in cirrhotic or non-cirrhotic livers accompanies a significantly higher risk of developing HCC, especially in the presence of HBsAg. (Author abstract) (10 Refs)

48. HEPATOCELLULAR CARCINOMA AND HEPATITIS-B-VIRUS: MORE ON THEIR RELATIONSHIP (MEETING ABSTRACT).

de Franchis R, Primignani M, Vecchi M, Zannier PM, Colombo M, Colucci G, Tommasini M
Clinica Medica III, University of Milano, Milan, Italy
Gastroenterology; 80(5,part2):1329 1981

To evaluate the strength of the association of Hepatocellular Carcinoma (HCC) with current or past Hepatitis-B-Virus (HBV) infection, serum HBV markers were studied in three groups of age and sex-matched patients: (a) 33 subjects with HCC, b) 33 patients with chronic active hepatitis and c) 33 hospitalized controls. Sera were tested for hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc, anti-HBc titre, HBeAg and anti-HBe by radioimmunoassay by means of commercially available kits (Abbott). The overall exposure rate to HBV (positivity for any one marker) was 94% in HCC, 85% in CAH, and 57% in controls. The prevalence of HBsAg was 36%, 12% and 9% in the three groups respectively. Prevalence of anti-HBs was much lower in HCC (3%) than in CAH (48%) and in controls (39%). Conversely, the prevalence of isolated anti-HBc positivity was 54% in HCC, 24% in CAH and 9% in controls. Serologic evidence of current HBV infection (HBsAg positivity, high-titre anti-HBc or HBeAg positivity) was more common in HCC (54%) than in CAH (18%) and controls (9%). The overall exposure rate to HBV is similar in HCC and CAH. However, serological evidence of continuing viral replication is much more common in the former group. A defective clearance of HBV in HCC is a possible explanation of the phenomenon. (no Refs)

49. PREVALENCE OF HEPATITIS B SURFACE ANTIGEN (HBSAG) AND ANTIBODY (ANTIHBS) IN PRIMARY LIVER CANCER DETERMINED BY RADIOIMMUNOASSAY AND PASSIVE HEMAGGLUTINATION TECHNIQUES (MEETING ABSTRACT).

Paulin RH, Piquet J, Seck SM, Tartarin O
No affiliation given
Eur J Nucl Med; 6:A23 1981

In previous studies from Senegal, HBsAg was found by agar gel diffusion or counterelectrophoresis techniques in serum of 39-42% of patients with primary liver cancer (PLC) as compared to 9-11% of controls. We report herein an investigation of the prevalence of HBsAg and antiHBs, utilizing in comparative trial the most sensitive of current assay methods. The study related to 164 subjects of black race from West Africa living in Senegal: 82 PLC matched with 82 age/sex hospitalized controls. HBsAg was determined by the Ausria II 125 test and antiHBs by the Ausab system: two solid phase radioimmunoassay procedures. The sera were also tested by passive hemagglutination assay (PHA). The serologic manifestations of HB are usual for PLC in Senegal. For each group the HBsAg and antiHBs frequencies were significantly higher with radioimmunoassay (RIA) than with PHA. The most important difference is registered for the controls. So, in order to value the prevalence RIA was the most sensitive procedure. Consequently, in PLC 71% against 17% in the controls very high level of contamination with the Australian antigen was observed a low immune response to surface antigen of the HB virus: presence of antibodies in 22% of the cases only among the PLC against 58% for the controls. This pattern found of the surface indicators in PLC fits in most cases with the unfavorable evolution of chronic hepatitis: persistance of HBsAg and no appearance of antiHBs antibodies. (2 Refs)

50. IMMUNOCHEMICAL REACTIVITY OF SIMIAN SARCOMA VIRUS POLYPEPTIDES ISOLATED BY PREPARATIVE SODIUM DODECYL SULFATE POLYACRYLAMIDE GEL ELECTROPHORESIS.

Johnson JC, Higuchi T, Geissler E
Dept. Biological Sciences, Old Dominion Univ., Norfolk, VA, 23508
Can J Microbiol; 27(2):238-242 1981

The polypeptides associated with a zonal centrifugation purified simian sarcoma virus propagated in lymphoblastoid NC-37 cells were isolated by preparative polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS) using a procedure designed to minimize the loss of immunochemical reactivity. The proteins p10, p15, p28, p36, p44, p75, and p86 were obtained in large yield and high degree of homogeneity. The electrophoretically purified p28 was analyzed by competition radioimmunoassay using antiserum to a pore exclusion and ion exchange purified simian sarcoma virus p28. Complete competition was observed with extracts of simian sarcoma virus infected cells. No competition was observed with uninfected or unrelated, infected cell extracts. The antigen-antibody affinity as measured by the slope of the competition curve using antiserum to p28 and 125I-labeled and electrophoretically purified p28 was the same as that for the p28 released from sonication-disrupted simian sarcoma virus. The data indicates that preparative purifications by polyacrylamide gel electrophoresis in the presence of SDS may be generally applicable for the isolation of proteins with essentially the same immunospecificities and affinity for a specific antiserum as proteins isolated by procedures that avoid the use of SDS and electrophoresis. (Author abstract) (21 Refs)

51. ANTIBODIES IN HUMAN SERA REACTIVE AGAINST AN INTERNAL STRUCTURAL PROTEIN OF HUMAN T-CELL LYMPHOMA VIRUS.

Kalyanaraman VS, Sarngadharan MG, Bunn PA, Minna JD, Gallo RC
(c/o Gallo) Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Nature; 294(5838):271-273 1981

A limited survey was designed to determine whether natural antibodies reactive against the human retrovirus isolate, HTLV, can be detected in human sera. The assay involved use of a radioimmune precipitation of 125I-labeled HTLV-cr p24 by human sera using a double antibody system. The p24 of HTLV-cr was purified to homogeneity from density-banded virus and radiolabeled with 125I. Serum from patient CR (the source of the isolate) and serum from another patient, MJ, with Sezary syndrome showed high reactivity to HTLV-cr p24. Twenty-one sera from various T-cell malignancies and 50 sera from random normal donors showed no significant precipitating activity. Eleven sera from close family members of patients with T-cell malignancies and previous evidence of HTLV infection were studied. Only one, from the wife of patient CR, reacted strongly in the immunoprecipitation. The antibodies against p24 are present in human sera, and these are specifically directed at HTLV-cr proteins and not at cell-specific determinants. Thus, the immunological reactions are not those reported in human sera against animal virus glycoproteins which, lacking virus specificity, are directed against the carbohydrate residues of the glycoprotein. The antibodies against HTLV are thus the first evidence for a specific immune response in humans against a retrovirus. (15 Refs)

52. INHIBITORS OF MONOCYTE RESPONSES TO CHEMOTAXINS ARE PRESENT IN HUMAN CANCEROUS EFFUSIONS AND REACT WITH MONOCLONAL ANTIBODIES TO THE P15(E) STRUCTURAL PROTEIN OF RETROVIRUSES.

Cianciolo G, Hunter J, Silva J, Haskill JS, Snyderman R
Lab. Immune Effector Function, Duke Univ. Medical Center, Durham, NC, 27710
J Clin Invest; 68(4):831-844 1981

Individuals with cancer have previously been shown to have abnormal chemotactic responsiveness. Surgical removal of the tumor often resulted in normalization of monocyte function, which suggests that human neoplasms might inhibit monocyte chemotaxis by release of soluble mediators. We therefore examined the effects of cancerous effusions on monocyte polarization, ie, the rapid change in monocyte morphology from round to a triangular 'motile' configuration in response to chemoattractants. All 17 malignant effusions, representing 15 tumor types, inhibited monocyte polarization induced by the chemoattractant N-formyl-methionyl-leucyl-phenylalanine by 45-89% (mean 55.9 +-12.7%, p less than 0.01) in blinded assays. None of 17 benign effusions significantly inhibited polarization (0-15% mean 6.2 +-4.2%). Dilutions of cancerous effusions as low as 1:200 produced inhibition that was time, temperature, and dose dependent. Monocyte polarization induced by activated serum or by chemotactic lymphokine was also blocked by cancerous effusions. The inhibitory activity affected the monocyte directly, and did not destroy the chemoattractant or block the polarization of granulocytes to chemotactic factors. High pressure liquid chromatography of five cancerous fluids revealed three peaks of inhibitory activity: greater than or equal to 200,000, 46,000 +-13,000, and 21,000 +-3,000 daltons. Fractionation of noncancerous effusions revealed only small amounts of the highest mol wt inhibitory activity. The inhibitory activity in cancerous effusion was heat stable (56 C, 30 min), trypsin sensitive, and could be adsorbed by three different monoclonal antibodies reactive to P15(E), a structural component of Type C retroviruses. In contrast, six monoclonal antibodies with other specificities had no effect on the inhibitors of polarization. This study demonstrates that human cancerous effusions contain novel proteins that are potent inhibitors of monocyte function and that are recognized by antibodies reactive to the P15(E) component of retroviruses. By producing such factors tumor cells may subvert monocyte-mediated surveillance. (Author abstract) (40 Refs)

53. RETROVIRUS P30-RELATED ANTIGEN IN HUMAN SYNCYTIOTROPHOBLASTS AND IGG ANTIBODIES IN CORD-BLOOD SERA.

Suni J, Wahlstrom T, Vaheri A
Dept. Virology, Univ. Helsinki, 00290 Helsinki 29, Finland
Int J Cancer; 28(5):559-566 1981

Sensitive immunological techniques were used to detect retrovirus markers in human pregnancy. A total of 1,540 human cord-blood sera were tested for retrovirus-reactive IgG antibodies using solid-phase enzyme immunoassay and purified RD114 virus as antigen. Of these, 118 (7.7%) sera were positive. Blocking assays with specific animal anti-p30 sera, use of control antigen, and electrophoretic protein experiments combined with immunological detection indicated that the human antibodies reacted specifically with the p30 protein. The occurrence of antibodies in cord-blood serum had a highly significant correlation to complications during pregnancy and also correlated to the number of previous absorptions and stillbirths. When goat anti-RD 114 p30 serum was used in the peroxidase-anti-peroxidase tissue staining procedure, p30-related antigen was detected in sections of all placental specimens (early and term pregnancies, blighted ova, hydatidiform moles, destructive moles and choriocarcinomas). However, in each case only syncytiotrophoblastic cells were positive. These findings, supplemented with different types of blocking tests, lead us to conclude that retrovirus p30-related antigen is selectively expressed in the highly differentiated syncytiotrophoblasts, which in the normal placenta are directly exposed to maternal blood. It is suggested that retrovirus-reactive antibodies may represent an autoimmune-like immune response to the p30-related syncytiotrophoblast antigen escaping during cellular damage. (Author abstract) (32 Refs)

54. ELISA FOR THE DETECTION OF ANTIGENS CROSS-REACTING WITH PRIMATE C-TYPE VIRAL PROTEINS (P30,GP70) IN HUMAN LEUKEMIC SERA.

Hehlmann R, Schetters H, Erfle V
Institut fur Biologie, Ingolstadter Landstrasse 1, 8042 Neuherberg, W. Germany
Haematol Blood Transfus; 26:530-536 1981

The enzyme linked immunosorbent assay (ELISA) was employed in the detection and quantification of the core protein p30 of murine leukemia viruses (MuLV), the baboon endogenous virus (BaEV) and simian sarcoma virus (SSV) and the envelope glycoprotein p70 of SSV. ELISA was successfully applied in detection and quantification of p30 in tissue culture cells, tumor cells, and sera. It was also used successfully when applied to the viral glycoprotein of SSV gp70. Reactivity of gp70 was not altered by glycosidases. Proteins reacting with antibodies against p30 of BaEV and SSV were specifically detected in leukemic sera, but not, or at only very low levels, in sera from non-leukemic patients and healthy controls. Cross-reacting antigens were detected with anti-SSV p30 IgG in 15/49 leukemic sera and with anti-BaEV-p30 IgG in 19/49 leukemic sera. Antigens cross-reacting with viral envelope glycoprotein of SSV were detected in both normal and leukemic sera. In a study of the sera of 23 patients with chronic myelogenous leukemia in blast crisis, 16 were positive for one or more structures cross-reacting with SSV gp70. The fact that many of these 16 patients had a shorter survival than the non-reactors suggests a possible prognostic role for these antigens. (19 Refs)

55. CELL FUSION AS A TOOL FOR THE DETECTION OF VIRAL FOOTPRINTS IN CHILDHOOD LEUKEMIA.

Jore J, Dubbes R, Coolen J, Nooter K
No affiliation given
Haematol Blood Transfus; 26:527-529 1981

Seven bone marrow samples from leukemic children were fused with fetal dog thymus A7573 cells and two samples were fused with rabbit cornea SIRC cells. Fused cultures were screened periodically for the presence of viral antigens by indirect cytoplasmic immunofluorescence assay (IFA), using antiviral antisera for the major 30,000 dalton internal polypeptide of murine type C virus (R-MuLV) and of primate type C virus (SiSV). Antigens appeared in 7/9 cultures 1-5 wk after fusion. IFA reaction was predominantly with SiSV antiserum: end point titers (reciprocal of highest antiserum dilution with which virus-specific cytoplasmic fluorescence was still observed) were in the range 40-80 vs less than 10-20 with R-MuLV antiserum and 10 in virus negative controls. Antigen presence was transient; after 2-3 mo the cultures were negative in the IFA. Fused cultures did not produce extracellular reverse transcriptase. Repetition of three fusion experiments with a hypoxanthine-guanine phosphoribosyl transferase mutant of A7573 offered the possibility of selection for hybrid cells, but selection did not result in higher IFA titers or reverse transcriptase production. Results show that the frequency of antigen positive cultures is comparable with that found in cocultivation experiments. However, cell fusion appears superior in that it speeds the appearance of antigens with cell passage number (1-5 wk after fusion vs 1-2 mo after starting cocultivation). The cell fusion procedure never led to overt virus production. (5 Refs)

56. ADULT T-CELL LEUKEMIA: ANTIGEN IN AN ATL CELL LINE AND DETECTION OF ANTIBODIES TO THE ANTIGEN IN HUMAN SERA.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 78(10):6476-6480 1981

Indirect immunofluorescence of certain human sera demonstrated an antigen(s) in the cytoplasm of 1-5% of the cells of a T-cell line, MT-1, from a patient with adult T-cell leukemia (ATL), which is endemic in southwestern Japan. The antigen was not detected in other human lymphoid cell lines, including six T-cell lines, seven B-cell lines, and four non-T non-B cell lines. The antigen did not show cross antigenicity with that of herpesviruses, including Epstein-Barr virus, herpes simplex virus, cytomegalovirus, varicella-zoster virus, herpesvirus saimiri, and Marek disease virus. The proportion of antigen-bearing cells was increased by a factor of approx five on culture in the presence of 5-iodo-2'-deoxyuridine. Antibodies against the antigen in MT-1 cells were found in all 44 patients with ATL examined and in 32 of 40 patients with malignant T-cell lymphomas (most of them had diseases similar to ATL except that leukemic cells were not found in the peripheral blood). The antibodies were also detected in 26% of the healthy adults examined from ATL-endemic areas but in only a few of those examined from ATL-non-endemic areas. On electron microscopy, extracellular *Type C virus* particles were detected in pelleted MT-1 cells cultured in the presence of 5-iodo-2'-deoxyuridine. (Author abstract) (26 Refs)

VIRAL STUDIES IN HUMAN CANCER

57. HERPES SIMPLEX VIRUS TYPE 2 AND CERVICAL CANCER.

Rapp F
Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA
Curr Probl Cancer; 6(4):1-18 1981

Infection with Herpes Simplex Virus (HSV)-1 can produce a spectrum of diseases, including fever blisters, herpes keratitis, and encephalitis. HSV-2 produces lesions of the genitalia as well as several serious infections of the newborn. There is an associated risk of cervical carcinoma in HSV-2-infected females. Mean antibody titers of HSV-2 in women with carcinoma of the cervix in situ were higher in women less than 40-yr-old than for control age-matched women. Mean titers of dysplasia patients and controls were the same in all age groups, however. In one study, of 530 women with normal cervical epithelium who had cervical smears taken, 47 (9%) had HSV-2 antigens in their cervical cells. Colposcopic examinations revealed abnormalities in two of these. Punch biopsies in the remaining 45 women revealed 36 normal, five hyperplasias, three metaplasias, and one cervical dysplasia. It will be important to determine if any of the 36 normal women develop cervical cancer in the future. HSV-2 has been shown to transform hamster cells in vitro. (41 Refs)

58. RESEARCH ON THE HERPESVIRUS SIMPLEX IN UTROCERVICAL CARCINOMA CARRIERS; A COMPARATIVE CLINICAL, VIRAL AND CYTOLOGICAL STUDY.

Souen JS, Gomes LF, Salvatore CA
Obstetrics and Gynecology, Hosp. das Clinicas, Univ. S. Paulo, Sch. Medicine, Ave. Dr. Eneas Carvalho Aguiar, 255, Cep 05403 Sao Paulo, Brazil
Rev Latinoam Oncol Clin; 13(1):9-12 1981

Cervical cancer (CC) patients were tested for evidence of herpes simplex virus-2 (HSV-2) and results compared with those from normal controls. During the period 1975-1976, 30 women in whom colposcopic evaluation did not reveal abnormalities and complementary colpocytology was negative, and 30 patients with documented CC confirmed by positive specimen were studied. Clinical, viral cytopathological, and cytological examinations sought evidence of herpetic infection. Neither direct signs of HSV-2 infection nor cytopathic alterations in rabbit corneal cells cultured with cervical smear specimens were observed for any of the women. Cytological alteration suggestive of HSV-2 infection was seen in 2/30 CC patients and 0/30 controls. Past and family herpetic history was noted in 2/30 CC patients and 4/30 controls. The differences were not significant. Results did not reveal a correlation between any of the HSV-2 aspects studied and CC. Immunological studies are recommended. (23 Refs)

59. IMMUNOPATHOLOGY OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

Purtilo DT
Dept. Pathology, Univ. Massachusetts Medical Center, Worcester, MA, 01605
Haematol Blood Transfus; 26:207-214 1981

Immunopathologic studies of affected individuals and carrier females from 25 kindreds exhibiting the X-linked lymphoproliferative syndrome (XLP) were carried out. XLP is a combined, variable immune deficiency with four phenotypes, all apparently triggered by Epstein-Barr virus (EBV) infection: (1) fatal infectious mononucleosis (IM), (2) chronic IM progressive to malignant lymphoma, (3) acute IM progressive to acquired agammaglobulinemia, and (4) malignant lymphoma. The clinical and pathological manifestations of XLP mimic the graft-versus-host reaction. Cytogenetic studies have revealed a spectrum from no appreciable defects to extensive aneuploidy in both peripheral lymphocytes and early passage lymphocytic lymphosarcoma cells; both affected and carrier individuals show a propensity to chromosome damage. Only weakly reactive anti-EBV antibodies are found, and anti-EBV nuclear antigen is lacking in affected individuals. Specific histopathology of the four phenotypes is discussed. These findings support the hypothesis that in XLP an immune deficiency toward EBV permits chronic and fatal lymphoproliferative responses to EBV infection. If this hypothesis is accurate, genetic counseling, providing of high titer gamma globulin, and antiviral therapy may be of prophylactic use. (58 Refs)

60. EPSTEIN-BARR VIRUS: ITS SITE OF PERSISTENCE AND ITS ROLE IN THE DEVELOPMENT OF CARCINOMAS.

Wolf H, Wilmes E, Bayliss GJ
Max v. Pettenkofer-Institut, Pettenkoferstrasse 9a, 8000 Munchen 2, W. Germany
Haematol Blood Transfus; 26:191-196 1981

A review of the role of Epstein-Barr virus (EBV) in carcinoma is presented. The site of EBV persistence in the body, the antibodies to EBV-specified antigens in carcinomas of the postnasal space and other locations within the Waldeyer's ring, and the cell-fusion ability of EBV-infected cells are detailed, and the possible significance of these findings is discussed. (27 Refs)

61. EPIDEMIOLOGIC, ETIOLOGIC AND IMMUNOLOGIC ASPECTS OF NASOPHARYNGEAL CARCINOMA (NPC).

Gastpar H, Wilmes E, Wolf H
Univ. ENT Clinic, Pettenkoferstr. 8a, D-8000 Munich 2, W. Germany
J Med; 12(4):257-284 1981

Epidemiologic studies indicate that mainland Chinese, especially those living in the South-East provinces, and overseas Chinese have the highest incidence of nasopharyngeal carcinoma (NPC) in the world. Most of the NPCs in this high-risk population are squamous cell carcinomas. Genetic and environmental factors implicated in NPC etiology are discussed, including HLA profiles, a putative second locus antigen (Sin-2) found in high-risk Chinese, environmental carcinogens, and vitamin A deficiency. Evidence for the role of ***Epstein-Barr virus*** (EBV) in NPC is presented. NPC patients have high antibody titers against all EBV antigens, and viral DNA has been detected in NPC epithelial cells. Early EBV infections may increase the likelihood of lymphocyte EBV induction and activation by environmental factors. (110 Refs)

62. CLUES TO PATHOGENESIS OF EPSTEIN-BARR VIRUS-INDUCED DISEASES FROM ANALYSIS OF 100 CASES OF X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP) (MEETING ABSTRACT).

Purtilo D, Sakamoto K, Barnabei V, Seeley J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Comprehensive analysis of 100 cases in the Registry of XLP revealed four major phenotypes after Epstein-Barr virus (EBV) infection: 1) infectious mononucleosis (IM) including 42 fatal cases without coexisting phenotypes and 32 with other phenotypes; 2) all 18 cases of aplastic anemia occurred with IM or malignant lymphoma (ML) and never did aplastic anemia occur simultaneously with agammaglobulinemia; 3) 32 cases of ML (B cell types only) including 16 cases solely and 16 with IM; and 4) agammaglobulinemia affected 16 boys, usually with IM or ML. Rarely, 3 phenotypes occurred simultaneously. Males have profound T and B cell and natural killer cell immune defects to EBV. Several carrier females exhibit IgA and IgM anti-viral capsid antigen and anti-early antigen indicating persistent infection due to their partial immunodeficiency of XLP. Our molecular hybridization studies of tissues of seven XLP patients reveal EBV genome in all cases. Approaches to diagnosis of XLP and related disorders and rationale bases for therapy are developing as a result of these studies. (no Refs)

63. INTEGRATION OF HEPATITIS B VIRUS DNA INTO THE GENOME OF LIVER CELLS IN CHRONIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA. STUDIES IN PERCUTANEOUS LIVER BIOPSIES AND POST-MORTEM TISSUE SPECIMENS.

Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC
Dept. Medicine, Liver Res. Center, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY, 10461
N Engl J Med; 305(18):1067-1073 1981

Recombinant-DNA technology combined with gel electrophoresis was used to find hepatitis B virus DNA (HBV-DNA) in liver and tumor tissue from patients with hepatocellular carcinoma and chronic liver disease, and to study integration of HBV-DNA into the genome of the tissue cells. HBV-DNA analysis was performed on hepatocellular carcinomas from 20 patients, all of whom had at least one serological marker indicating intercurrent or previous HBV infection. Twelve patients whose sera were positive for hepatitis B surface antigen (HBsAg) had integrated HBV-DNA in the tumor; 3/8 who were HBsAg negative but positive for antibody to HBsAg (anti-HBs) also had HBV-DNA integration. Five patients who were HBsAg negative but anti-HBs positive had no detectable HBV-DNA in their tumors. In some patients integrated HBV-DNA was also found in nontumorous liver tissue with the same or different hybridization pattern from that of tumor. In five HBsAg carriers with evidence of the carrier state and chronic liver disease for less than 2 yr, HBV-DNA was present but not integrated in liver tissue. In two patients who carried HBsAg for greater than 8 yr, HBV-DNA was integrated into the host genome. The studies suggest that integration of HBV-DNA into hepatocytes occurs during the course of persistent hepatitis B virus infection and precedes development of gross neoplasm. (22 Refs)

64. AN AUTOPSY STUDY OF HEPATOCELLULAR CARCINOMA IN HONG KONG.

Ho J, Wu PC, Kung TM
Pathology Dept., Univ. Hong Kong, Queen Mary Hosp. Compound, Hong Kong, Hong Kong
Pathology; 13(3):409-416 1981

Two hundred and eighty-seven autopsy cases of hepatocellular carcinoma (HCC) in Chinese were reviewed. The analyses included histological study of the tumor and of the non-cancerous liver tissue, the cause of death and metastases. Bleeding of esophageal varices was most frequent but rupture of tumor less common in cases associated with cirrhosis than in those without cirrhosis. There was a significantly higher incidence of bilobar involvement by tumor in the clear cell type of HCC and in cases unassociated with cirrhosis compared to other histological types of HCC and HCC with cirrhosis, possibly because of longer survival of the former groups. A strong association was found between cirrhosis and hepatic fibrosis with HCC and hepatitis B surface antigen (HBsAg), suggesting an oncogenic effect of chronic persistent ***hepatitis B virus*** (HBV) infection on hepatocytes. (Author abstract) (16 Refs)

65. EPISOMAL SIMIAN VIRUS 40 GENOMES IN HUMAN BRAIN TUMORS.

Krieg P, Amtmann E, Jonas D, Fischer H, Zang K, Sauer G
(c/o Sauer) Inst. Virus Res., German Cancer Res. Center, 6900 Heidelberg, W. Germany
Proc Natl Acad Sci USA; 78(10):6446-6450 1981

Eight out of 35 human intracranial tumors were shown by restriction enzyme analysis to contain unintegrated simian virus

40 (SV40) DNA molecules. The relative amount of viral DNA was estimated to be the equivalent of one viral genome within every 10th to 20th cell. No infectious virus was detected in tissue cultures established from the tumors. From only one tumor was it possible to rescue, by cell fusion, infectious SV40 displaying wild-type properties. In those cases that permitted a more detailed analysis, the restriction enzyme cleavage patterns appeared to correspond to the wild-type patterns with one exception, in which the SV40 episomes displayed a deletion of approx 70 base pairs close to the origin of DNA replication. From one tumor, the SV40 genomes were transferred into permissive CV-1 monkey cells by transfection with the total tumor DNA. Despite their persistence as episomes no infectious virus was produced. Furthermore, no viral antigens were detectable, although the SV40 messengers for the small and the large tumor antigens were present. These cells had, however, acquired the ability to form colonies in lower concentrations of serum. Thus this report provides, by restriction enzyme analysis, direct evidence for the presence of SV40 DNA in human tumors. (Author abstract) (34 Refs)

66. REGULATION OF HUMAN T-CELL PROLIFERATION: T-CELL GROWTH FACTOR AND ISOLATION OF A NEW CLASS OF TYPE-C RETROVIRUSES FROM HUMAN T-CELLS.

Gallo RC, Poiesz BJ, Ruscetti FW
NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:502-514 1981

Recent results with human T-cell growth factor (TCGF), the various T cell systems, and the isolation of a new type-C retrovirus released from growing T-cells from some of these T-cell neoplasias are summarized. Unlike normal T-cells, neoplastic mature T-cells respond directly to TCGF without prior lectin or antigen in vitro activation. Transformed T-cell lines exhibit phenotypic characteristics consistent with the neoplastic cells of their disease of origin. A new retrovirus, human T-cell lymphoma-leukemia virus (HTLV) was isolated from fresh and cultured cells from two patients, each with a variant of a cutaneous T-cell lymphoma. Further studies showed that HTLV was not significantly related to any known animal retrovirus, is not an endogenous (genetically transmitted) virus of man, and at present is only associated with fresh or cultured T-cells from patients with the T-cell neoplasia. The results suggest that HTLV infected some mature T-cells of some people and may be involved in some neoplasias involving these cells. (33 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

67. REPRESSION AND ACTIVATION OF THE GENOME OF HERPES SIMPLEX VIRUSES IN HUMAN CELLS.

Wigdahl BL, Isom HC, Rapp F
(c/o Rapp) Dept. Microbiology and Specialized Cancer Res. Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Proc Natl Acad Sci USA; 78(10):6522-6526 1981

We have described previously a cell culture system in which the herpes simplex virus (HSV) Type 2 (HSV-2) genome is maintained in a repressed form after treatment of infected cells with 1-beta-D-arabinofuranosylcytosine and increase of incubation temperature from 37 C to 39.5 C. Infectious HSV-2 production was activated by altering incubation temperature or by superinfecting with human cytomegalovirus. We now report the establishment of an analogous system utilizing HSV Type 1 (HSV-1). Human embryo lung cells were infected with HSV-1 and treated with 1-beta-D-arabinofuranosylcytosine (25 ug/ml) for 7 days to minimize both synthesis of virus DNA and infectious virus while allowing expression of early virus genes. HSV-1 was maintained in an undetectable form for at least 72 days when the incubation temperature was raised from 37 C to 40.5 C after removal of the inhibitor. HSV-1 gene expression was then predictably turned on by superinfection with human cytomegalovirus or by reducing the incubation temperature. Virus replicated after activation was compared with the respective parental virus with regard to inhibition by the HSV-1-specific antiviral (E)-5-(2-bromovinyl)-2'-deoxyuridine and EcoRI, HindIII, and Xba I restriction endonuclease cleavage patterns. The results show activation of HSV gene expression in human cells by a human cytomegalovirus early gene function(s), followed by synthesis of parental-like HSV. (Author abstract) (24 Refs)

68. INHIBITION OF DNA SYNTHESIS IN RELATION TO ENHANCED SURVIVAL OF UV-DAMAGED HERPES VIRUS IN MONKEY CELLS TREATED BY A VARIETY OF 2-NITRONAPHTHOFURANS.

Nocentini S, Coppey J, Buisson JP, Royer R
Service de Radiologie-Cancerologie, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex 05, France
Mutat Res; 90(2):125-135 1981

The effects of various 2-nitronaphthofuran (2NNF) derivatives on immediate inhibition of normal DNA synthesis and on the capacity of pretreated CV-1 monkey kidney cell cultures to support replication of UV-damaged Herpes simplex virus (HSV) were investigated. The capacity of treated cultures (40 hr) to support the production of intact virus was inhibited by approx 20% at concentrations eliciting max enhancement of UV-HSV production and by approx 60% at concentrations 3.3x higher. In contrast, after 40 hr of contact with the various compounds, the production of UV-damaged HSV was enhanced. After treatment of cultures with drug concentrations giving greatest reactivation in terms of virus yield, the proportion of cells infected by UV-damaged HSV giving rise to infectious centers was increased. The inhibition of DNA synthesis induced by four representative 2NNF compounds was found to be irreversible at least during the first 4-5 hr of post-treatment incubation; inhibition increases with time. The most efficient 2NNF derivatives, especially 2-nitro-7-methoxynaphtho[2,1-b]furan-R7000, were at least as potent as aflatoxin B1 in inducing virus reactivation. The results indicate that 2NNFs are DNA-damaging agents like chemical carcinogens. (21 Refs)

69. ACYCLOVIR TREATMENT OF EPSTEIN-BARR VIRUS (EBV) INDUCED POST-TRANSPLANT LYMPHOMA (MEETING ABSTRACT).

Hanto DW, Sakamoto K, Purtilo D, Balfour HH, Simmons RL, Najarian JS
University of Minnesota, Minneapolis, MN, 55455
Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; 1981

Lymphoma occurs in 0.7% of renal transplant recipients and the mortality is high (90%). No effective therapy has been reported. Acyclovir (ACV) an anti-viral agent, has promise to this application in light of our evidence that EBV is the cause of these tumors. A transplant developed a tumor in lymph nodes, tonsils, and bone marrow. Cell markers showed a B cell proliferation producing Ig of polyclonal specificity (IgM, IgG, and IgG, kappa and lambda). Staining for EBV nuclear antigen was positive and cyclic RNA/DNA filter hybridization demonstrated 3 EBV genome equivalents per tumor cell. Oropharyngeal shedding of EBV was shown. ACV for 7 days resulted in a dramatic objective and subjective response; EBV shedding disappeared. Forty-eight hr after stopping ACV, fever, symptoms, and objective tumor growth recurred. A second ACV course resulted in resolution lasting 3 mo. A polyclonal B cell recurrence responded to ACV. One mo later a third recurrence, resistant to ACV, resulted in patient death. Cell markers demonstrated sIg/cIg of the IgG kappa class only. ACV is effective during the polyclonal growth phase of these EBV induced lymphomas. The tumor probably evolved into a monoclonal neoplasm which was resistant to ACV. This is the first documented in vivo effect of ACV on EBV. (no Refs)

GENERAL REVIEWS

70. ONCOGENIC VIRUSES.

Wyke JA
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Pathol; 135(1):39-85 1981

Virus-induced cancer in animals, including man, and the molecular mechanisms of virus-induced neoplasia are reviewed. Topics discussed include the diversity of relationships between oncogenic viruses and host animals, the problem of identifying human tumor viruses, and a brief catalogue of clinically important oncogenic viruses (avian retroviruses, murine leukemia and sarcoma viruses, leukemia and sarcoma viruses of other species, mouse mammary tumor virus, retroviruses and nonneoplastic disease, papovaviruses, adenoviruses, lymphotropic herpesviruses, other herpesviruses, hepatitis B virus, and poxviruses). General features of the interactions between viruses and their host cells, the transformed cell, replication of retroviruses, and cell transformation and tumor formation by retroviruses are discussed. (85 Refs)

71. B-LYMPHOTROPIC PAPOVAVIRUS (LPV) -- INFECTIONS OF MAN?

Brade L, Gissman L, Mueller-Lantzsch N, Zur Hausen H
Institut fur Virologie, Zentrum fur Hygiene, Hermann-Herderstrasse 11, 7800 Frieburg i. Br., W. Germany
Haematol Blood Transfus; 26:204-206 1981

Papovavirus-like particles that were first observed in supernatants of Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines from African green monkeys (AGM) were isolated and characterized. The host range for this virus consisted only of B-lymphoblasts from AGM and from one EBV-negative human cell line (line BJA-B), giving this virus the tentative designation lymphotropic papovavirus (LPV). LPV DNA is slightly smaller than SV40 DNA, weighing 3.2 x 10(6) daltons; it yields very different fragments than does SV40 DNA when these two DNA species are digested with Hae III enzyme. After greater than 1 yr of continuous passage in BJA-B cells, the LPV DNA became very heterogenous when examined by gel electrophoresis, apparently due to the accumulation of defective DNA molecules. LPV differs antigenically from all papovaviruses characterized so far. When human sera were tested for antibody to LPV, only about 10% of individuals less than 29 yr old were positive, whereas approx 30% of individuals greater than 30 yr old were positive. No disease-specific reactivity for LPV has so far been demonstrated, although some correlations between the presence of LPV antibodies in the sera and symptoms involving the lymphatic system have been noted. LPV may represent a new subgroup of papovaviruses that could have a role in proliferative diseases of the lymphatic system. (9 Refs)

OTHER RELATED STUDIES

72. HERPES SIMPLEX INFECTION IN ACUTE MYELOGENOUS LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES: A PROSPECTIVE STUDY.

Lam MT, Pazin GJ, Armstrong JA, Ho M

(c/o Ho), Univ. Pittsburgh, A427 Crabtree Hall, Pittsburgh, PA, 15261

Cancer; 48(10):2168-2171 1981

To better define the frequency and clinical characteristics of herpes simplex virus (HSV) infection in adult patients with acute myelogenous leukemia (AML), the authors prospectively studied 29 patients undergoing remission induction chemotherapy with twice weekly throat wash cultures for an av of 25.3 days. Ten seropositive patients (34.5%) shed HSV at least once. Eight patients were asymptomatic. Two episodes of herpes labialis were severe and persistent, but no visceral dissemination was observed. Reactivation of HSV infections in AML patients presumably with marked immunosuppression occurs, but less frequently and more benignly than has been suggested. Daunomycin and cytosine arabinoside, which can inhibit HSV replication, may have accounted for this lower frequency of reactivation. (Author abstract) (13 Refs)

73. IMMUNOLOGIC MONITORING IN BREAST CANCER PATIENTS RECEIVING POSTOPERATIVE ADJUVANT CHEMOTHERAPY.

Strender LE, Blomgren H, Petrini B, Wasserman J, Forsgren M, Norberg R, Baral E, Wallgren A

Radiumhemmet, Karolinska Hosp., S1-104 01 Stockholm, Sweden

Cancer; 48(9):1996-2002 1981

A group of 17 patients, having undergone modified radical mastectomy for breast cancer, received 12 cycles of chemotherapy with methotrexate, 5-fluorouracil, and chlorambucil during 17 mo. The number of circulating T and non T lymphocytes, as defined by E, EAC, and ME rosette formation, were reduced during treatment. The Non-T lymphocytes, however, were reduced to the highest relative extent. Relative phytohemagglutinin and mixed lymphocyte culture responses of the cells decreased, whereas purified protein derivative responses were unchanged. Serum concentrations of IgM were reduced, but IgA and IgG concentrations were unchanged or slightly increased. Antibody titers to morbilli and herpes simplex were not changed, whereas the antibody activity against cytomegalovirus (CMV) increased in several seropositive patients. None of these patients, however, developed signs of a CMV infection. (Author abstract) (37 Refs)

74. CHRONIC INFLAMMATORY BOWEL DISEASE: ABSENCE OF ADENOVIRUS DNA AS ESTABLISHED BY MOLECULAR HYBRIDIZATION.

Roche JK, Wold WS, Sanders PR, Mackey JK, Green M
Duke Univ. Medical Center, Box 3252, Durham, NC, 27710
Gastroenterology; 81(5):853-858 1981

Because previous evidence indicated that adenovirus is tropic for gut wall cells (particularly terminal ileum) and can become chronically established in mammalian cells as a latent infection, we examined, through the use of sensitive molecular hybridization techniques capable of detecting minute amounts of adenovirus DNA, the hypothesis being that adenovirus is specifically associated with both Crohn's disease and ulcerative colitis. DNA of 21 coded specimens from 17 operated patients (6 with Crohn's disease, 4 with ulcerative colitis, 7 controls) was hybridized with each of five [32P]DNA probes, prepared by nick translation of adenovirus DNA with Escherichia coli polymerase I and representative of each major adenovirus subgroup (A through E). While quantities as small as 0.2 copies of purified adenovirus DNA per human cell were detectable in standardization experiments, none of the test specimens was positive, either in Crohn's disease or ulcerative colitis, whether histologically normal or abnormal. Potential sources of false-negative results were analyzed and judged to be unlikely. Future investigation in this area may await the development of more sensitive assays for viral DNA or for evidence of new candidate virus systems. (Author abstract) (34 Refs)

75. SUPPRESSIVE EFFECTS OF INTERFERON ON CELL FUSION BY SENDAI VIRUS.

Tomita Y, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 55(part2):289-295 1981

Suppressive effects of human IFN-alpha, IFN-beta and mouse-IFN on syncytium formation in human and mouse transformed cells have been studied using UV-irradiated Sendai virus (UV-Sendai virus). After treatment of human RSa cells with 500 units/ml human IFN-alpha for 16 hr, the syncytium formation induced by UV-Sendai virus was reduced to less than 10% of controls. The suppressive effect was dependent on the amount of interferon added, and it was blocked by the addition of cycloheximide. Suppression of syncytium formation was also observed on human IFr cells, which are partially resistant to the anticellular effect of interferon but are sensitive to the antiviral effect of interferon. Human IFN-beta also had a suppressive effect on syncytium formation in human transformed cells, and human IFN-alpha, IFN-beta and mouse IFN showed species specificity in their effect on fusion. This anti-cell fusion activity was developed in IFr cells from about 5 hr after addition of IFN-alpha and when the cells were treated with IFN-alpha for 16 hr, the resistant state of cells continued for over 20 hr after removal of IFN-alpha. (Author abstract) (32 Refs)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. CHARACTERIZATION OF THE EPSTEIN-BARR VIRION-ASSOCIATED DNA POLYMERASE AS ISOLATED FROM SUPERINFECTED AND DRUG-STIMULATED CELLS.

Clough W, McMahon J
Molecular Biology Div., Univ. Southern California, Los Angeles, CA, 90007
Biochim Biophys Acta; 656(1):76-85 1981

We reported previously that Epstein-Barr (EB) virions and detergent-treated nucleocapsids co-purified with significant amounts of DNA polymerase activity that did not resemble

HE 20. 3173/2:

other known host or viral polymerases. We report here that this species of DNA polymerase activity is present at early times after infection in lymphocytes abortively lytically infected (superinfected) with EB virus. However, studies with [35S]methionine labeling suggest de novo synthesis of enzyme has not occurred. Conversely, drug-stimulated lymphocytes that synthesize EB viral late proteins and virions contain this species of polymerase to the virtual exclusion of all others. This EB viral polymerase shows a marked preference for nicked and gapped double-stranded rather than primed single-stranded DNA templates. Its processiveness as measured on primed phiX174 phage DNA template is lower than that of lymphocyte beta polymerase. The data reported here are consistent with the hypothesis that the EB virion-associated DNA polymerase is synthesized at late times in the viral life cycle as are other structural proteins but it plays an important role early after viral infection. It is known that mature herpes virion DNA (including that of EB virus) is nicked and gapped and we propose that this virion polymerase repairs the viral DNA at an early stage in infection before viral DNA replication begins. (Author abstract) (41 Refs)

2. ANTIGENIC AND STRUCTURAL CONSERVATION OF HERPESVIRUS DNA-BINDING PROTEINS.

Littler E, Yeo J, Killington RA, Purifoy DJ, Powell KL
Dept. Microbiology, Univ. Leeds, Leeds LS2 9JT, England
J Gen Virol; 56(part2):409-419 1981

Previously, we have shown a common antigen of several herpesviruses (pseudorabies virus, equine abortion virus and bovine mammillitis virus) to be antigenically related to the major DNA-binding proteins of herpes simplex virus Types 1 and 2. In this study we have purified the cross-reacting polypeptide from cells infected with pseudorabies virus, equine abortion virus and bovine mammillitis virus and shown the cross-reacting protein to be a major DNA-binding protein for each virus. Tryptic peptide analysis of the cross-reacting DNA-binding proteins of all five viruses has shown structural similarities. The proteins thus were shown to share common antigenic sites, to have similar biological properties and to have a highly conserved amino acid sequence. This unexpected similarity between proteins from diverse herpesviruses suggests an essential and fundamental role of the major DNA-binding protein in herpes virus replication. (Author abstract) (28 Refs)

3. MALIGNANT TUMOURS IN TUPAIA (TREE SHREW).

Hofmann W, Moller P, Schwaier A, Flugel RM, Zoller L, Darai G
Pathologisches Institut, Universitat Heidelberg, Im Neuenheimer Feld 220, D-6900 Heidelberg 1, W. Germany
J Med Primatol; 10(2/3):155-163 1981

Nine spontaneous malignant tumors of the tree shrew were detected and analyzed during an observation period of 9 yr. The tumors were histopathologically examined and classified. All tumors developed in imported tupaia only. From the tumor cells of two different animals new tupaia herpesviruses were isolated. This is the first report on spontaneous malignant tumors of tupaia in captivity. (Author abstract) (11 Refs)

4. TYPE 5 ADENOVIRUS ISOLATED FROM URINE OF PATIENT WITH HODGKIN'S DISEASE.

Trifajova J, Bruckova M, Ryc M, Lukasova M
Inst. Hygiene and Epidemiology, Srobarova 48, 100 43 Praha, Czechoslovakia
J Hyg Epidemiol Microbiol Immunol; 25(3):321-323 1981

An adenovirus of typical electronoptic morphology, serologically identified as type 5, was isolated from urinary sediment in a patient with Stage IIIB Hodgkin's disease. Antibodies against the isolate were demonstrated by means of virus neutralization, complement fixation, and gel immunodiffusion. Assays were performed in serum specimens collected from the patient over several yr both before and after isolation. Serological evidence indicating persistent adenovirus type 5 infection was thus obtained despite the absence of clinical signs of urinary tract disease. (8 Refs)

5. PROTEIN KINASES ASSOCIATED WITH THE ADENOVIRUS SINGLE-STRANDED DNA-BINDING PROTEIN.

Cajean-Feroldi C, Loeb J, Meguenni S, Girard M

Unites de Physiologie des Virus et de Biochimie des Regulations, Institut de Recherches Scientifiques sur le Cancer, Boite postale 8, F-94800 Villejuif, France

Eur J Biochem; 120(1):79-87 1981

Protein kinase activities copurifying with the 72,000-Mr DNA-binding protein of adenovirus on DNA-cellulose chromatography and gel filtration in acrylamide/agarose have been partially characterized and purified. One of these kinases was found to phosphorylate efficiently the viral DNA-binding protein in vitro and to be stimulated severalfold by the addition of histones, protamine, or polyamines. The kinase does not, however, phosphorylate histones, protamine, casein, or phosvitin. A second protein kinase was also recovered from single-stranded DNA-cellulose which is able to phosphorylate the 72,000-Mr DNA-binding protein, but which is inhibited by the addition of histones. Phosphorylation in vitro of the 72,000-Mr DNA-binding protein from the ts125 mutants of adenovirus by the histone-stimulated protein kinase was found to be thermosensitive. (Author abstract) (52 Refs)

6. USE OF MONOCLONAL ANTIBODIES AS PROBES OF SIMIAN VIRUS 40 T ANTIGEN ATPASE ACTIVITY.

Clark R, Lane DP, Tjian R

Dept. Biochemistry, Univ. California, Berkeley, CA, 94720

J Biol Chem; 256(22):11854-11858 1981

We have investigated the ATPase activity of simian virus 40 (SV40) large T antigen by using monoclonal antibodies as specific probes of enzymatic activity. Three hybridoma cell lines secreting anti-T antigen antibodies were derived from mice that were immunized with D2 T antigen, an SV40 T antigen-related protein. Monoclonal antibodies secreted by these hybridomas bind to three distinct T-antigen determinants. In order to bind to T antigen, the three antibodies required amino acid residues coded by the region of the A gene between 0.37 and 0.29 map unit. Two of these antibodies (DL3C3 and DL3C4) strongly inhibited T antigen ATPase activity. The third antibody (DL3C5) only weakly inhibited the ATPase activity possibly by decreasing the affinity of T antigen for ATP. These results demonstrate that the ATPase activity is intrinsic to T antigen and suggest that the ATPase function of T antigen maps on SV40 A gene between 0.37 and 0.29 map unit. A T antigen-specific ATPase assay capable of detecting low levels of T antigen in crude extracts of SV40 infected cells was developed by using 3C5 to immobilize an active form of the enzyme. These results indicate that monoclonal antibodies can be used as probes of enzyme structure and function. (Author abstract) (37 Refs)

7. TYPE D RETROVIRUSES FROM HUMAN CELLS DO NOT CONTAIN A MINOR GLYCOPROTEIN SHARED BY OLD WORLD MONKEY TYPE D VIRUSES.

Wunderlich V, Uckert W
Dept Virology,, Central Inst. Cancer Res., Academy Sciences German Democratic Republic, Berlin, E. Germany
Arch Virol; 70(1):43-53 1981

The protein patterns of Type D retroviruses isolated either from permanent human cells (HeLa virus, HeLaV, and HEp-2 virus, HEp-2V) or from spectacled langur (langur virus, LV), an Old World monkey, were investigated using sodium dodecyl sulfate polyacrylamide gel electrophoresis. Labeling with 14C-amino acids and 3H-glucosamine revealed for each of these isolates five polypeptides with mol wt of 10,000, 12,000, 15,000, 25,000 and about 68,000 and identified the 68,000 D-protein as a glycoprotein. An additional glycoprotein with a mol wt of 20,000 (gp20) was resolved in LV similarly as in previous studies with Mason-Pfizer monkey virus. However, in accordance with our recent analysis of a third Type D isolate from human cells (PMFV), gp20 was not detectable in both HeLaV and HEp-2V regardless of the cell line in which they were grown. Thus, it appears that the Type D virus isolates from human cells are slightly distinct from the presently known type D retroviruses of Old World monkeys. The relevance of this finding to the origin of the human isolates, however, remains to be shown. (Author abstract) (31 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

8. AN EPSTEIN-BARR VIRUS EARLY PROTEIN INDUCES CELL FUSION.

Bayliss GJ, Wolf H
Max von Pettenkofer Inst., Pettenkoferstrasse 9a, 8000 Munich 2, W. Germany
Proc Natl Acad Sci USA; 78(11,part2):7162-7165 1981

Superinfection of Raji cells with Epstein-Barr virus (EBV) leads to syncytium formation. Studies using metabolic inhibitors and amino acid analogues suggest that the fusion-inducing factor belongs to the early group of virus-specified proteins. Induction of early EBV protein synthesis in Raji cells by using various chemicals also leads to syncytium formation, indicating that the fusion process is not caused by a virion membrane protein introduced into the cells upon infection. The relevance of these findings to the association of EBV with carcinoma of the nasopharynx is discussed. (Author abstract) (25 Refs)

9. THE SITE OF INTEGRATION OF THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE IN HUMAN CELLS TRANSFORMED BY AN HSV-1 DNA FRAGMENT.

Kit S, Hazen M, Otsuka H, Qavi H, Trkula D, Dubbs DR
Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030
Int J Cancer; 28(6):767-776 1981

To analyze the site of integration of the herpes simplex virus Type I (HSV-I) thymidine kinase (TK) gene in biochemically transformed human cells, TK- HeLa(BU25) cells were transformed to the TK+ phenotype by a cloned, 2 kbp PvuII fragment of HSV-1 DNA. The transformed cells [HeLa(BU25)/TF pAGO PP3] were fused with mouse LM(TK-) cells, and human-mouse somatic cell hybrid clones (LH PP3 clones 1, 2, 3, 5 and 6) were isolated in HATG-ouabain selective medium. The HeLa(BU25)/TF pAGO PP3 cells and the LH PP3 hybrid clones expressed HSV-1-specific TK activity and a herpesvirus-associated nuclear antigen, and contained herpesvirus nucleotide sequences. Molecular hybridization experiments were carried out to map the HSV-I and flanking cellular nucleotide sequences in the biochemically transformed cells. TK- revertant subclones isolated by growing the LH PP3 clone 5 cells in BrdUrd (and diphtheria toxin) failed to form colonies in HATG medium, but retained HSV-I nucleotide sequences. Isozyme analyses on 21 gene-enzyme systems representing 21 human chromosomes revealed that all of the LH PP3 clonal lines expressed human hexosaminidase B, which has been assigned to chromosome 5, and all were sensitive to diphtheria toxin, which is also a marker for chromosome 5. Chromosome analyses showed that chromosome 5 was the only human chromosome present in mitoses of LH PP3 clone 5 cells and that human chromosome 5 was present in most of the mitoses of LH PP3 clone 1, 2, 3, and 6 cells. The latter clones also contained 1 or 2 additional human chromosomes in some of the cells. As expected from the molecular hybridization analyses, TK- revertants of LH PP3 clone 5 cells retained portions of chromosome 5 and expressed human hexosaminidase B. The results indicate that HSV-I nucleotide sequences were stably integrated in the biochemically transformed cells, most likely in human chromosome 5. (50 Refs)

VIRUS REPLICATION AND EXPRESSION

10. THE STABILITY OF EARLY ADENOVIRUS MRNA IS CONTROLLED BY THE VIRAL 72 KD DNA-BINDING PROTEIN.

Babich A, Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 26(3,part1):371-379 1981

H5ts125, a temperature-sensitive mutant of adenovirus type 5, is restricted to the early phase of infection when grown at the nonpermissive temperature. One phenotype of the virus is the overproduction of early viral mRNA at the nonpermissive temperature relative to levels found in wild-type-infected cells, although normal levels are found at the permissive temperature. We have analyzed this phenomenon for the production of RNA from two specific early viral transcription units, E1A and E1B. Transcription rates from both of these regions were found to be the same in ts125-infected cells as in wild-type-infected cells at the nonpermissive temperature. However, when the cytoplasmic stabilities of the E1A and E1B mRNAs were measured in wild-type- and ts125-infected cells, it was found that at the nonpermissive temperature, the RNAs were 3 to 5x more stable in a ts125 infection than in a wild-type infection. Since the mutation in ts125 maps to the gene for the 72 kd DNA-binding protein, these results imply that a functional 72 kd protein is required for the rapid turnover of early viral mRNA in wild-type-infected cells, indicating that the abundance of early viral mRNA is controlled by the 72 kd DNA-binding protein. (Author abstract) (54 Refs)

11. ADENOVIRUS DNA REPLICATION IN VITRO: PURIFICATION OF THE TERMINAL PROTEIN IN A FUNCTIONAL FORM.

Enomoto T, Lichy JH, Ikeda JE, Hurwitz J
Dept. Physiological Chemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Tokyo 113, Japan
Proc Natl Acad Sci USA; 78(11,part2):6779-6783 1981

The 80,000-dalton form of the adenovirus (Ad) terminal protein (pTP) has been purified from Ad-infected HeLa cells. pTP was assayed by its ability to form a covalent complex with dCMP. The protein copurified with an activity that is essential for in vitro Ad DNA replication (Ad protein activity) as well as with a DNA polymerase activity that was distinguished from those of HeLa cell DNA polymerase alpha, DNA polymerase beta, and DNA polymerase gamma. The Ad protein-associated DNA polymerase activity was detected with activated DNA but not with poly(rA).oligo(dT) as template and was insensitivie to aphidicolin and sensitive to N-ethylmaleimide. The Ad protein, DNA polymerase, and pTP-dCMP complex-forming activities sedimented in a glycerol gradient as a single peak with an apparent molecular size of 180,000 daltons. NaDodSO4/polyacrylamide gel analysis of the glycerol gradient fraction showed major bands of 80,000 and 140,000 daltons. The 80,000-dalton band was identified as pTP by comparison of its tryptic peptide map with that of the 55,000-dalton form of the terminal protein, which was purified from Ad virions. (Author abstract) (23 Refs)

12. STRUCTURE OF CHROMATIN AT DEOXYRIBONUCLEIC ACID REPLICATION FORKS: PRENUCLEOSOMAL DEOXYRIBONUCLEIC ACID IS RAPIDLY EXCISED FROM REPLICATING SIMIAN VIRUS 40 CHROMSOMES BY MICROCOCCAL NUCLEASE.

Cusick ME, Herman TM, DePamphilis ML, Wassarman PM
Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA, 02115
Biochemistry; 20(23):6648-6658 1981

Replicating simian virus 40 (SV40) chromsomes were found to be similar to other eukaryotic chromosomes in that the rate and extent of micrococcal nuclease (MNase) digestion were greater with replicating than with nonreplicating mature SV40 chromatin. MNase digestion of replicating SV40 chromsomes, pulse labeled in either intact cells or nuclear extracts, resulted in the rapid release of nascent DNA as essentially bare fragments of duplex DNA (3-7 S) that had an av length of 120 base pairs and were degraded during the course of the reaction. The small nascent DNA fragments released from replicating chromosomes represented prenucleosomal DNA (PN-DNA) from the region of replication forks that encompasses the actual sites of DNA synthesis and includes Okazaki fragments. Predigestion of replicating SV40 chromosomes with both Escherichia coli exonuclease III (3'-5') and bacteriophage T7 gene 6 exonuclease (5'-3') resulted in complete degradation of PN-DNA. This result, together with the observation that isolated PN-DNA annealed equally well to both strands of SV40 restriction fragments, demonstrated that PN-DNA originates from both sides of replication forks. Over 90% of isolated Okazaki fragments annealed only to the retrograde DNA template. The characteristics of isolated PN-DNA were assessed by examining its sensitivity to MNase and single strand specific S1 endonuclease, sedimentation behavior before and after deproteinization, buoyant density in CsCl after formaldehyde treatment, and size on agarose gels. In addition, it was observed that MNase digestion of purified SV40 DNA also resulted in the release of a transient intermediate similar in size to PN-DNA, indicating that a DNA-protein complex is not required to account for the appearance of PN-DNA. These and other data provide a model of replicating chromosomes in which DNA synthesis occurs on a region of replication forks that is free of nucleosomes and is designated as prenucleosomal DNA. (57 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

13. SITE-SPECIFIC INVERSION SEQUENCE OF THE HERPES SIMPLEX VIRUS GENOME: DOMAIN AND STRUCTURAL FEATURES.

Mocarski ES, Roizman B
Marjorie B. Kovler Viral Oncology Lab., Univ. Chicago, 910 East 58th St., Chicago, IL, 60637
Proc Natl Acad Sci USA; 78(11,part2):7047-7051 1981

The genome of herpes simplex virus-1 consists of two covalently linked components, L and S, that invert relative to each other. The L and S components consist of unique DNA sequences bracketed by inverted repeats. The inverted repeats of the L component are designated ab and b'a' and those of the S component are designated a'c' and ca. the number of a sequences at the termini and at the L-S component junction varies from one to several copies. Insertion into the middle of the L component of a DNA fragment consisting of 156 base pairs (bp) of the b sequence, an entire a sequence of 501 bp, and 618 bp of the c sequence created a new site through which additional inversions in the genome occurred. Comparison of the nucleotide sequences of DNA fragments containing one and two a sequences defined the domain of the a sequence. The single a sequence consists of two 20-bp direct repeats (designated as DR1) bracketing a region that contains 19 tandem direct repeats of a 12-bp sequence (DR2) adjacent to three direct repeats of a 37-bp sequence (DR4), in addition to short stretches of unique sequences. The fragment with two tandem a sequences contained three copies of DR1-ie, the intervening DR1 was shared by the two a sequences. Furthermore, one a sequence contained 22 copies of DR2 and two copies of DR4 whereas the second a sequence contained 19 copies of DR2 and two copies of DR4. These observations suggest that (i) amplification of the number of terminal and internal a sequences is the consequence of intramolecular or intermolecular recombination through DR1, (ii) the number of copies of DR2 and DR4 within the a sequence is not fixed and may vary as a consequence of unequal crossing over or slippage, and (iii) inversion results from intramolecular recombination between terminal and inverted a sequences. (Author abstract) (16 Refs)

14. INABILITY TO RESCUE VIRAL GENES FROM HUMAN CELLS BIOCHEMICALLY TRANSFORMED BY HERPES SIMPLEX VIRUS TYPE 2 DNA.

Campione-Piccardo J, Rawls WE
Dept. Pathology, McMaster Univ., Hamilton, Ontario L8N 3Z5, Canada
Can J Microbiol; 27(10):1123-1128 1981

Thymidine kinase negative (TK-) mutants of HSV-1 were used to attempt to rescue HSV-2 genes from cells biochemically transformed with HSV-2DNA. The results indicate that the occurrence of a rescue event was less than 7 x 10(-7) in this system. (Author abstract) (31 Refs)

15. CLONED FRAGMENTS OF HUMAN ADENOVIRUS TYPE-12 DNA.

Vogel S, Brotz M, Kruczek I, Neumann R, Eick D, Winterhoff U, Doerfler W
Inst. Genetics, Univ. Cologne, D-5000 Cologne 4, W. Germany
Gene; 15(2/3):273-278 1981

The cloning of EcoRI, BamHI, HindIII, and PstI restriction fragments of adenovirus type 12 (Ad12) DNA is described. EcoRI fragment A was found to contain the right terminal 5 kilobase pairs of Ad12 DNA including the terminal 143 base pairs. (26 Refs)

16. SYNTHESIS OF AN UNSPLICED CYTOPLASMIC MESSAGE BY AN ADENOVIRUS 5 DELETION MUTANT.

Carlock L, Jones NC
(c/o Jones) Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907
Nature; 294(5841):572-574 1981

A mutant of adenovirus 5 (dl502) which contains a deletion within early region Ela and prevents splicing of the normal Ela transcripts is described. Mapping of cytoplasmic RNA isolated from wild-type and dl502-infected HeLa cells indicated that an unspliced Ela message is synthesized and accumulates in the cytoplasm of dl502-infected cells. Comparison of the Ela-generated autoradiograph bands from wild-type and dl502 RNA preparations showed that the unspliced Ela product from dl502 accumulates in the cytoplasm to 25-50% of the levels of wild-type Ela products. It is thought unlikely that the unspliced message could have resulted from nuclear leakage. Two phenotypic properties of dl502 indicated that a defective, partially functional, Ela gene product was being synthesized. Increased synthesis of dl502, which is defective for growth on HeLa cells, was attributed to the synthesis of a partially functional Ela gene product required for productive growth, by dl502. The second indicator was detection of transcripts from other regions of the genome, although seen at reduced levels. The results indicated that an unspliced region Ela transcript accumulates in the cytoplasm of dl502-infected cells; splicing and the removal of intron sequences are not necessary prerequisites to the production of stable, cytoplasmic RNA from this particular gene. (27 Refs)

17. NUCLEOTIDE SEQUENCES OF 5' TERMINI OF ADENOVIRUS 2 EARLY TRANSFORMING REGION E1A AND E1B MESSENGER RIBONUCLEIC ACIDS.

Hashimoto S, Wold WS, Brackmann KH, Green M
Inst. Molecular Virology, St. Louis Univ. Medical Center, St. Louis, MO, 63110
Biochemistry; 20(23):6640-6647 1981

The major 5'-terminal RNase T1 oligonucleotides derived from human adenovirus type 2 (Ad2) early regions E1a and E1b were characterized and sequenced. Poly(A+) polyribosomal RNA was isolated from Ad2-infected KB cells cultured 10 h in the presence of cycloheximide, the 5'-terminal m7Gppp was removed, and the 5'-OH of the penultimate 2'-O-methylated nucleoside was labeled with [gamma-32P]ATP by using polynucleotide kinase. 5'-32P-labeled poly(A+) RNA was hybridized to EcoRI-A, HpaI-E, and HpaI-C and to cloned fragments representing map positions 0-4.5, 4.5-8, 8-10.7, 8-17, and 17-31.5. Fragment-specific mRNA was digested with RNase T1, the resulting oligonucleotides were resolved by two-dimensional paper electrophoresis-homochromatography, and the 5'-terminal methylated oligonucleotides were characterized by nuclease P1 digestion and two-dimensional thin-layer chromatography. Two major 5'-terminal RNase T1 oligonucleotides were obtained from EcoRI-A-specific mRNA; these were characterized by RNase T2 digestion and two-dimensional thin-layer chromatography and were sequenced by partial nuclease P1 digestion and electrophoresis-homochromatography. These two oligonucleotides were mapped to E1a and E1b, respectively, by analysis of E1a- and E1b-specific mRNA. Their sequences are as follows: E1a, m7G pp(m6)AmC(m)UCUUGp; E1a,m7Gppp(m(6))AmC(m)UCUUGp;
E1b,m7Gppp(m(6))AmC(m)AUCUGp, in which the methylations shown in parentheses are partial. The E1a 5'-terminal oligonucleotide was found as a minor component of E1b mRNA, implying that mRNAs exist with both E1a and E1b sequences. Five other minor 5'-terminal oligonucleotides were observed in E1 mRNA, implying that transcription initiation is not always precise. Sequences corresponding to these two 5' termini were found at nucleotide positions 498-504 (E1a) and 1699-1705 (E1b) in the Ad2 DNA sequence, positions where the 5'-terminal region of E1a and E1b mRNAs has been mapped by nuclease gel analysis and electron microscopic visualization. (50 Refs)

18. THE HIGH AFFINITY BINDING SITE ON POLYOMA VIRUS DNA FOR THE VIRAL LARGE-T PROTEIN.

Gaudray P, Tyndall C, Kamen R, Cuzin F
Centre de Biochimie du CNRS, Universite de Nice, 06034 Nice, France
Nucleic Acids Res; 9(21):5697-5710 1981

In order to map the high affinity binding site for the viral large-T protein on polyoma virus DNA, we have developed an assay which does not require purified protein. It is based on the specific elution of the large-T ATPase activity for calf thymus DNA cellulose by recombinant DNA molecules including known sequences of the viral DNA. Using this assay, a high affinity binding site has been mapped on the early region side of the ori region. Binding requires the integrity of a sequence /AGAGGC/TTCC/AGAGGC/ (nucleotides 49 to 64 in the DNA sequence of the A2 strain). Similar repeats of a PuGPuGGC sequence within less than 20 bases are not found within the viral coding regions, but are strikingly common in the control regions of papovaviruses and other eukaryotic DNAs. (Author abstract) (31 Refs)

19. THE SV40 72 BASE REPAIR REPEAT HAS A STRIKING EFFECT ON GENE EXPRESSION BOTH IN SV40 AND OTHER CHIMERIC RECOMBINANTS.

Moreau P, Hen R, Wasylyk B, Everett R, Gaub MP, Chambon P
Laboratoire de Genetique Moleculaire, Faculte de Medecine, Institut de Chimie Biologique, 11 Rue Humann, 67085 Strasbourg, France
Nucleic Acids Res; 9(22):6047-6068 1981

By introduction of recombinant plasmids into monkey CV1 cells, we have unambiguously demonstrated that sequences entirely within the 72 bp repeat, which is located upstream of the SV40 early region, are crucial for T-antigen expression in vivo. We have also shown that a DNA fragment containing the 72 bp repeat, inserted directly before chicken conalbumin or adenovirus-2 major late promoter sequences in chimeric plasmids where these promoters replace that of the SV40 early genes, caused a dramatic increase in the expression of T-antigen in vivo. This effect was independent of the orientation of the 72 bp repeat, but was sensitive to its location within the plasmid.

When the 72 bp repeat was separated from the promoter sequences, T-antigen expression was reduced. Insertion of the 72 bp repeat into equivalent plasmids containing no known eukaryotic promoter sequences (plasmids which were not detectably expressed in vivo) gave rise to a measurable, but smaller level of expression. The stimulation of expression by the 72 bp repeat is cis-acting: it required covalent linkage to the recombinant. We discuss the possibility that the 72 bp repeat region in SV40 may act as a bi-directional entry site for RNA polymerase B such that promoter sequences linked to the repeat are more efficiently utilized. (Author abstract) (41 Refs)

20. LOCALIZATION OF ONCOGENE IN DNA OF SIMIAN ADENOVIRUSES. II. IDENTIFICATION IN SV20 DNA OF SPECIFIC FRAGMENT WITH TRANSFORMATION ACTIVITY.

Parkhomenko II, Denisova TS, Sitnikov BS
Lab. Physicochemical Basis of Oncology, Inst. Chemical Physics, Moscow, USSR
Tsitologiia; 23(9):1026-1030 1981

DNA of simian adenovirus SV20 was subjected to hydrolysis with the specific restriction endonucleases EcoRI, BamHI, XbaI, and HindIII. Transformation activity of DNA fragments produced by the BamHI was similar to that of the intact DNA. Absence of transformation activity in the fragments produced by the EcoRI indicated the left terminal position of the oncogene in the virus genome. (11 Refs) (In RUS)

IMMUNOLOGICAL STUDIES

21. IDENTIFICATION OF ANTIGENIC DETERMINANTS UNIQUE TO THE SURFACES OF CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Kintner C, Sugden B
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Nature; 294(5840):458-460 1981

Four monoclonal antibodies (anti-EBVCS) that detect antigenic determinants unique to the surfaces of Epstein-Barr virus (EBV)-transformed cells but are not associated with virus production were isolated. Cell lines transformed in vitro or those transformed in vivo but not associated with Burkitt's lymphoma bound anti-EBVCS strongly, whereas cell lines from patients with Burkitt's lymphoma bound them at intermediate levels or not at all. When untreated lymphocytes and lymphocytes exposed to EBV, Concanavalin A, and pokeweed mitogen were assayed, only EBV-exposed lymphocytes expressed EBVCS determinants, which were detectable within 48 hr after infection. Assay of unseparated populations of EBV-exposed primary lymphocytes and immunoglobulin-positive and -negative populations indicated that those cells which express EBVCS determinants are separated as B cells along with those which express the EBV-induced nuclear antigen and that the two antigen-expressing populations are overlapping and may be identical. A polypeptide with an apparent mol wt of 45,000 was precipitated from an EBVCS-positive cell line and was likely to be the molecule which carries EBVCS determinants. The results indicate that EBVCS determinants are expressed at reduced levels on cell lines established from Burkitt's lymphoma patients relative to expression on other EBV-transformed cell lines. EBVCS determinants are among possible determinants recognized by autochthonous, cytotoxic T cells specific for EBV-transformed cells and may therefore be equivalent to lymphocyte determined membrane antigen (LYDMA); this possibility was supported by the finding that EBVCS and LYDMA were expressed with the same time course in lymphocytes infected with EBV in vitro. If the EBVCS determinants are used by cytotoxic T cells to identify their targets, reduced expression of EBVCS on Burkitt's lymphoma cell lines is consistent with these tumor cells having been selected in vivo to survive that cytotoxic response. (18 Refs)

22. STUDIES ON LONG-TERM T-CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR VIRUS IN IMMUNOSUPPRESSED RENAL ALLOGRAFT RECIPIENTS.

Crawford DH, Edwards JM, Sweny P, Hoffbrand AV, Janossy G
Human Tumor Immunology Group, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England
Int J Cancer; 28(6):705-709 1981

Peripheral blood lymphocytes from normal seropositive donors and renal transplant recipients on various immunosuppressive regimens have been tested for their ability to mount a cytotoxic response when cultured with autologous EB virus-infected B cells and thereby to cause regression of proliferating B-cell foci. Cultures from 10 normal seropositive donors all showed the normal pattern of regression. Lymphocytes from patients receiving Cyclosporin A therapy with or without prednisolone completely failed to cause regression, thus allowing B-cell lines to proliferate unchecked. Cells from 2 of 17 patients treated with azathioprine and prednisone also failed to cause regression. The cells from the remaining 15 individuals showed regression responses varying from minimal to normal. These results suggest a mechanism by which EB virus-related tumors may arise in immunosuppressed renal allograft recipients. (Author abstract) (34 Refs)

23. CELLULAR AND HUMORAL IMMUNITY IN HODGKIN'S DISEASE: I. PATIENTS IN CONTINUOUS LONG-TERM REMISSION.

Skovmann-Sorensen O, Schroder H, Moller-Larsen A, Haahr S
(c/o Haahr) Inst. Medical Microbiology, Univ. Aarhus, Bartholin Building, DK-8000 Aarhus C, Denmark
Scand J Haematol; 27(3):171-180 1981

Cell-mediated and humoral immunity to herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella zoster virus (VZV) were examined in 37 patients with Hodgkin's disease in continuous long term remission. This group had lower blast-transformation than a matched control group to all three antigens. Patients originally showing B-symptoms had higher transformation to VZV than those with A-symptoms. Patients treated with irradiation only had higher transformation than those treated with either chemotherapy or a combination of chemotherapy and irradiation. There was a clear tendency towards lower transformation in patients having been in remission for 2 yr or less. Phytohemagglutinin (PHA) stimulation gave lower response in the patient group than in the control group. Patients with B-symptoms had lower response than those with A-symptoms. Interferon production was specially impaired in patients with B-symptoms. The patient group had higher CF titers against HSV and CMV while the control group had higher titers against VZV. B-symptom patients had higher titers against VZV than A-symptom patients. It is concluded that HD patients have impaired immune function many years after discontinuation of therapy, but there are certain differences regarding the in vitro immunity within the patient groups. (Author abstract) (17 Refs)

24. HERPESVIRUS ANTIGENS AS MARKERS FOR CERVICAL CANCER.

Grpta PK, Aurelian L, Frost JK, Carpenter JM, Klacsmann KT, Rosenshein NB, Tyrer HW
Dept. Pathology, John Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Gynecol Oncol; 12(2,part2):S232-S258 1981

A total of 393 patients representing cervical atypias, cancers, and nonneoplastic disease have been studied. Cellular specimens have been stained with antisera raised against total herpes Type 2 virus (HSV-2) and subfractions labeled crude AG-e, pure AG-e, ICP 12, and ICP 14. Reproducibility, statistical significance, false positive and false negative results, specificity, and sensitivity of the various antisera have been investigated. Correlation of immunocytostaining with Papanicolaou staining has been made. Usefulness of these markers in the detection and diagnosis of premalignant and malignant cervical epithelial changes for mass screening has been discussed. Using crude AG-e, pure AG-e, HSV-2, and HSV-1 antisera in a number of blind studies, no significant differences were found in the reproducibility of results. Observations indicated that a minimum of 30 cells must be analyzed to make data amenable to statistical analysis. Exfoliated cells from 62, 75, 77, and 94% of patients respectively diagnosed as mild, moderate, and marked atypia, and cancer were studied with antisera against total HSV-2. Similar results were observed with antisera against pure AG-e. No patient reacted with anti-AG-e or anti-HSV-1 antiserum in the absence of reactivity to antisera against total HSV-2 antigens. Studies using anti-ICP 12 and -ICP 14 antigens established the wide and specific staining character of anti-HSV-2 antisera. Morphologic preservation of cells by Papanicolaou staining after the FA procedures was considered satisfactory for diagnostic purposes. Our studies indicated the potential usefulness of anti-HSV-2 and anti-AG-e antisera in mass cervical cancer screening programs and cytology automation. (Author abstract) (21 Refs)

25. MONOCLONAL ANTIBODIES AGAINST ADENOVIRUS TYPE 5: PREPARATION AND PRELIMINARY CHARACTERIZATION.

Russell WC, Patel G, Precious B, Sharp I, Gardner PS
Div. Virololgy, Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
J Gen Virol; 56(part2):393-408 1981

Eight different hybridoma cell lines producing monoclonal antibodies against the major antigens of human adenovirus Type 5 have been obtained. They were selected by screening initial hybridomas by the fluorescent antibody technique followed by radioimmune precipitation and they reacted with hexon, penton, fiber and 100K polypeptides. Five apparently different epitopes against the hexon antigen were detected showing a spectrum of activity against the hexons of other serotypes, suggesting that the hexon contained a variety of subgroup specificities as well as the previously described group and type specificities. (Author abstract) (26 Refs)

26. IMMUNOPEROXIDASE TECHNIQUE IN CRYOULTRAMICROTOMY FOR THE DETECTION OF SIMIAN ADENOVIRUS IN CELL NUCLEI.

Kuhlmann WD, Viron A
Experimental Medicine, Institut fur Nuclearmedizin/D.K.F.Z., Im Neuenheimer Feld 280, D-69 Heidelberg, W. Germany
Biol Cell; 41(2):153-155 1981

Refinements in the immunoperoxidase technique for labeling of viruses in ultrathin sections of nuclei are described. Simian adenovirus type 7 infected monkey kidney cells were used to localize virus antigens in cell nuclei. Pretreatment of sections with non-immune serum of the same species in which the 'sandwich' (sheep) antibodies were rinsed was effective in prevention of nonspecific adsorptions. Incubation times were also drastically shortened. (13 Refs)

VIRAL STUDIES IN HUMAN CANCER

27. THE SPECTRUM OF EPSTEIN-BARR VIRUS DISEASE.

O'Dell JR
Dept. Internal Medicine, Univ. Nebraska Medical Center, NE
Nebr Med J; 66(12):275-278 1981

History and pathogenesis of infectious mononucleosis (IM), chronic IM, and other lymphoproliferative syndromes caused by Epstein Barr virus (EBV) are discussed. Primary EBV infection occurs primarily during childhood and is usually asymptomatic. Transmission is through oropharyngeal secretion of EBV by a seropositive individual to a seronegative individual. IM usually persists for 25-30 days, but some individuals suffer from chronic IM possibly due to the presence of early antigen-R antibodies. Primary EBV infection that develops during adolescence can lead to x-linked recessive lymphoproliferative syndrome (Duncan's disease) or possibly Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. (5 Refs)

28. HERPESVIRUS: AGENT OF MANY ILLS.

Fuller E, Crumpacker C, Corey L, Gulnan M
Harvard Medical Sch., Boston, MA
Patient Care; 15(19):200-204,208-209,213,216-218,220-221,225-227 1981

Human herpesviruses include herpes simplex Types 1 and 2, varicella zoster, Epstein-Barr, and cytomegalovirus. Herpes simple Type 2, a sexually transmitted virus, is closely linked to cervical carcinoma, although current evidence is insufficient to prove that the virus is the causative agent. Acyclovir is being tested as a specific antiviral agent against herpesviruses. (8 Refs)

29. POSSIBLE ROLE OF HERPES VIRUS-2 IN ETIOLOGY OF CERVIX CARCINOMA.

Vasil'ev BV, Iovlev VI, Kniazev PG, Bokhman IaV, Smorodintsev AA
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Akush Ginekol (Mosk); (9):20-22 1981

Complement fixation tests showed significant increases in titers of specific antibodies against herpes simplex virus-2 (HSV-2) in the blood sera of patients with cervix carcinoma, compared with sera of healthy controls. The number of patients with high titers of antibodies against HSV-2 was 1.5-3x greater than the number with high titers against HSV-1. These findings confirm the role of HSV-2 in the etiology of cervix carcinoma. (10 Refs) (In RUS)

30. HERPES SIMPLEX VIRUS AND ORAL CANCER.

Cohen WL
Maxillofacial Clinic, Univ. California, Los Angeles, CA, 90024
Dent Hyg; 55(11):31-39 1981

Herpes simplex viruses are reviewed and evidence for association between herpes simplex virus type I and oral cancer is discussed. First reports of an association between HSV-I and oral cancer in 1957 (in 6 elderly patients who developed carcinoma of the lip at a site of frequent herpetic infection) were anecdotal. No confirming reports were published and two clinicians found no such association in their clinical practice. Establishment of such an association is difficult because of the interaction of other factors or cofactors in development of oral cancer, including ethnic background or genetic predisposition, and chemical or thermal carcinogens such as alcohol and tobacco. Other cofactors may include gummatous lesions of syphilis, chronic irritants (poorly fitting dentures), and environmental factors such as air and water pollution. (22 Refs)

31. DETECTION OF NUCLEIC ACID SEQUENCES IN CERVICAL TUMORS.

McDougall JK, Galloway DA, Crum C, Levine R, Richart R, Fenoglio CM
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Gynecol Oncol; 12(2,part2):S42-S55 1981

Our results suggest that HSV RNA is present in abnormal cells of a significant proportion of cervical tissue specimens containing intraepithelial neoplasia and that it is only rarely detected in sections of normal cervical epithelium. A proliferation of atypical basal-type cells and their continued persistence through the more mature upper layers is the first indication of dysplasia and CIN in cervical epithelium, and it is in these proliferating cells that evidence of HSV RNA can be found. The results of localizing an HSV-2 antigen (ICSP 11-12) closely parallel the in situ hybridization results. About 30% of patients with dysplasia (CIN I and II) have detectable antigen. It is interesting to note that the incidence of detectable antigen decreased to 12% in patients with carcinoma in situ, but was demonstrable in 20% of patients who had microinvasive or invasive squamous cell lesions. (Author abstract) (52 Refs)

32. CYTOMEGALY RETINITIS IN IMMUNE-SUPPRESSED PATIENTS.

Steinke B, Ostendorf P, Volker HE
Med. Univ.-Klinik, Abt. II, Otfried-Muller-Strasse, D-7400 Tubingen, W. Germany
Med Welt; 32(44):1658-1660 1981

Two cases of retinitis caused by cytomegaly virus (CMV) in immunosuppressed patients are reported. One patient had received a kidney transplant; the other was being treated for ovarian carcinoma. Both suffered vision loss. Suppression of the immune system increases the risk of infection and the severity of those infections that do occur. No safe and effective treatment for CMV retinitis has been developed. (43 Refs) (In GER)

33. PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN. EVIDENCE OF A NEW ACQUIRED CELLULAR IMMUNODEFICIENCY.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A
Dept. Medicine, UCLA Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024
N Engl J Med; 305(24):1425-1431 1981

An acquired T-cell immunodeficiency is reported in four previously healthy homosexual men. All patients experienced malaise, fever, and lymphadenopathy for several mo prior to onset of more specific symptoms. All contracted Pneumocystis carinii pneumonia, extensive mucosal candidiasis, and multiple viral infections. Cytomegalovirus was found in the secretions of all patients, and Kaposi's sarcoma developed in one patient 8 mo after he presented with esophageal candidiasis. Antibodies to Epstein-Barr virus and hepatitis B were detected in the other three. Monoclonal-antibody analysis of peripheral blood T-cell subpopulations revealed an inversion of the T helper to suppressor/cytotoxic ratio. The association between chronic cytomegalovirus infection and Kaposi's sarcoma is discussed, and a relationship between the immunodeficiency syndrome and the recent appearance of Kaposi's sarcoma in the male homosexual population is suggested. Cytomegalovirus infection could be a result rather than a cause of the T-cell defect; exposure to an undetected microorganism, drug, or toxin may have made these patients susceptible to infection by opportunistic organisms including cytomegalovirus. (41 Refs)

34. SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS.

Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschm an SZ, Cunningham-Rundles C, Adelsberg BR, Parham DM, Siegel M, Cunningham-Rundles S, Armstrong D
Mt. Sinai Medical Center, New York, NY, 10029
N Engl J Med; 305(24):1439-1444 1981

Cellular immunodeficiency associated with chronic perianal ulcerative herpes simplex lesions is reported in four homosexual men. Onset of the disease was characterized by malaise, fever, and wt loss. Later infections included cytomegalovirus, Pneumocystis carinii, and Candida albicans. One patient developed Kaposi's sarcoma. Skin anergy, lymphopenia, poor or absent responses to plant lectins and antigens in vitro, and depressed natural killer cell activity against target cells infected with herpes simplex virus were observed. An association may exist between primary cytomegalovirus infection and a particularly prolonged cellular immunodeficiency state. (29 Refs)

35. OPPORTUNISTIC INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Durack DT
Duke Univ. Medical Center, Durham, NC, 27710
N Engl J Med: 305(24):1465-1467 1981

Current data and theories concerning opportunistic infections and Kaposi's sarcoma in homosexual men are reviewed. Patients are typically young and live in large cities, and many use drugs. Infectious agents are low grade pathogens that often cause opportunistic infections in compromised hosts, and the death rate is very high. The immunodeficiency is cellular rather than humoral, and the gap in host defenses is not limited to those against any one class of microbe. Evidence of previous or current cytomegalovirus infection is a common finding.

Kaposi's sarcoma is found in young Africans, elderly Americans, renal-transplant recipients, and homosexual men. The discovery of cytomegalovirus genome in Kaposi's sarcoma tissue indicates the possibility of a cause-effect relationship between the virus and the tumor; some new factor may have distorted the host-parasite relation. Recreational drugs such as amyl nitrite may combine with the effects of persistent viral infection to cause immunosuppression in some genetically predisposed men. (16 Refs)

36. PAPILLOMAVIRUS INFECTIONS AND HUMAN GENITAL CANCER.

zur Hausen H, De Villiers EM, Gissmann L
Instut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Gynecol Oncol; 12(2,part2):S124-S128 1981

Possible role of human genital warts (GW) virus in genital cancer was investigated. Additional candidate viruses were analyzed for their possible involvement in this disease. Experiments designed to clarify the question of whether the papillomavirus (PV) found in GW is identical with PV observed in other skin papillomas led to identification of eight distinct types of human PV. Risk of malignant conversion is specifically correlated with specific types of PV. (34 Refs)

37. ASSOCIATION OF HUMAN PAPILLOMAVIRUS WITH NEOPLASTIC PROCESSES IN THE GENITAL TRACT OF FOUR WOMEN WITH IMPAIRED IMMUNITY.

Shokri-Tabibzadeh S, Koss LG, Molnar J, Romney S
(c/o Koss), Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Gynecol Oncol; 12(2,part2):S129-S140 1981

The presence of papillomavirus particles was documented by electron microscopy in atypical squamous epithelium of the cervix, vagina, and vulva, and in cells derived therefrom in four women with compromised immune status who were being followed in our clinics. Three of the patients had treated Hodgkin's disease, and one a dermatologic disorder, perhaps akin to epidermodysplasia verruciformis. Initially, all four patients developed treatment-resistant condylomata acuminata of the vulva and adjacent areas. Subsequently one of the patients was shown to harbor in the vagina a focus of markedly atypical epithelium, perhaps a flat condyloma. Two other patients, followed for several years, developed multiple epidermoid carcinomas in situ affecting the cervix, vagina, and vulva. In one of these two latter patients the disease progressed to multiple foci of superficially invasive carcinoma. The possible role of the human papillomavirus in the genesis of these lesions is discussed. (Author abstract) (39 Refs)

38. HUMAN PAPILLOMAVIRUS AND CANCER OF THE UTERINE CERVIX.

Meisels A, Morin C
Dept. Lab. Medicine, Saint-Sacrement Hosp., 1050 chemin Sainte-Foy, Quebec G1S 4L8, Canada
Gynecol Oncol; 12(2,part2):S111-S123 1981

Human papillomavirus infection of the cervix was found in 1.69% of 234,715 women during a mass screening program during the years 1975 to 1979 inclusive. Condylomata of the cervix represent the most prevalent squamous lesion diagnosed during this 5-yr period. Most of condylomata (71.16%) were found in women under 30 yr of age with a mean of 27.47 yr and a peak incidence of 2.5% in the 20-25 yr-age group. Condylomata precede invasive carcinoma by 27.45 yr. The coexistence of condylomata was observed in 25.6% of dysplastic and neoplastic lesions. This association seems to shorten the mean time for malignant transformation. The epidemiologic behavior of condylomata appears similar to dysplasia which is considered a precursor of neoplasia. However, the high regression rate of condylomata (68.39%) implies that lowered immunity and other promoting or synergistic factors are necessary for malignant conversion. (Author abstract) (123 Refs)

39. VIRUS PAPILLOMAS IN HUMANS.

Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981

Five major groups of papillomas (warts) that occur in humans and are caused by viruses are reviewed. The five groups are common warts (verruca vulgaris) and their subtypes, flat or juvenile warts (verruca plana), epidermodysplasia verruciformis (verrucosis generalisata), genital warts (condyloma acuminatum), and warts of mucous membranes. The forms of human papilloma virus (HPV) that are known to cause each type of wart are identified; it is noted that the HPV(s) that causes warts of the mucous membranes has not been identified. Each of the major groups of warts is described with regard to clinical features, subgroups, differential diagnosis, and treatment. The epidemiology, incubation times, histopathology, and morphology of the HPVs are considered also. It is noted that malignant transformation of some types of warts may occur; epidermodysplasia verruciformis, genital warts, oral papillomas, and papillomas of the larynx have all shown evidence of malignant potential. It is noted that, to date, only the HPV types 5 and 8 have been associated with malignant changes. The possibility that additional HPVs may have malignant potential is considered. (16 Refs) (In GER)

40. CLUSTERING OF HEPATITIS B VIRUS INFECTION AND HEPATOCELLULAR CARCINOMA IN A FAMILY.

Gilmore IT, Harrison JM, Parkins RA
Royal Liverpool Hosp., Liverpool L7 8XP, England
J R Soc Med; 74(11):843-845 1981

Family clustering of primary hepatocellular carcinoma (HCC) is well recognized, although rare. One possible reason for such clustering has become apparent since the advent of tests to detect circulating markers of hepatitis B virus infection, and this has been the common etiological factor in three families studied. We report the results of screening a Chinese family following the death of one member who had been found to have HCC associated with hepatitis B surface antigenemia. Four of seven siblings were traced: one had died of HCC 5 yr earlier, and evidence of past or present hepatitis B infection was found in the remaining three, one of whom was also found to have HCC. (Author abstract) (24 Refs)

41. HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS. A PROSPECTIVE STUDY OF 22,707 MEN IN TAIWAN.

Beasley RP, Lin CC, Hwang LY, Chien CS
Univ. Washington Medical Res. Unit, 15-2 Kung Yuan Road, Taipei, Taiwan
Lancet; 2(8256):1129-1133 1981

A prospective general population study of 22,707 Chinese men in Taiwan has shown that the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis B surface antigen (HBsAg) is much higher than among non-carriers (1,158/100,000 vs 5/100,000 during 75,000 man-yr of follow-up). The relative risk is 223. PHC and cirrhosis accounted for 54.3% of the 105 deaths among HBsAg carriers but accounted for only 1.5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the etiology of PHC. (Author abstract) (25 Refs)

42. LONG-TERM FOLLOW-UP OF PERSONS INADVERTENTLY INOCULATED WITH SV40 AS NEONATES.

Mortimer EA, Lepow ML, Gold E, Robbins FC, Burton GJ, Fraumeni JF
Dept. Epidemiology and Community Health, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
N Engl J Med; 305(25):1517-1518 1981

Mortality from cancer in children who received polio vaccine containing simian virus 40 (SV40) as neonates was investigated. Of 1073 infants less than 3 days old, 920 received live, attenuated, monovalent poliomyelitis vaccine (Sabin) orally and 153 received inactivated poliomyelitis vaccine (Salk) im. Annual follow-up over 17-19 yr, initiated upon realization of the presence of SV40 in preparations, revealed 15 deaths, all from identified causes, chiefly birth defects or trauma. No deaths from cancer had occurred, as compared with an expected mortality of one. A 15-yr-old girl had a mixed tumor of the salivary gland with a 'low degree of malignancy.' No recurrence has been noted 6 yr after surgery. Forty-five subjects have borne children, none with congenital anomaly at birth. In spite of several caveats, the findings are reassuring, since SV40 is carcinogenic in laboratory animals and produces subclinical infections in humans. (12 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

43. CORE (2'-5')OLIGOADENYLATE AND THE CORDYCEPIN ANALOG: INHIBITORS OF EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LYMPHOCYTES IN THE ABSENCE OF INTERFERON.

Doetsch PW, Suhadolnik RJ, Sawada Y, Mosca JD, Flick MB, Reichenbach NL, Dang AQ, Wu JM, Charubala R, Pfleiderer W, Henderson EE
(c/o Suhadolnik) Dept. Biochemistry, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Proc Natl Acad Sci USA; 78(11,part2):6699-6703 1981

The 3'-deoxyadenosine (cordycepin) analog of (2'-5')oligo(A) [(2'-5')oligoadenylate with a triphosphate at the 5' end], synthesized enzymatically from cordycepin 5'-triphosphate in lysed rabbit reticulocytes or L-cell extracts was (i) inhibitory to translation in lysed rabbit reticulocytes and (ii) metabolically stable in extracts of either L cells or C85-5C lymphoblasts. The 5' dephosphorylated (core) (2'-5')oligo(A) and the core cordycepin analog can replace human fibroblast interferon in preventing the transformation of human lymphocytes after infection with Epstein-Barr virus B95-8 (EBV) as determined by the decreased incorporation of [3H]thymidine into cellular DNA and the inhibition of morphological transformation of EBV-infected lymphocytes. Whereas the naturally occurring core (2'-5')oligo(A) was cytotoxic to uninfected lymphocytes and proliferating lymphoblasts, the core cordycepin analog was not. Human WBC interferon was more effective than human fibroblast interferon in the inhibition of EBV-induced transformation of human umbilical cord lymphocytes and adult peripheral blood lymphocytes. (Author abstract) (53 Refs)

44. INHIBITION OF PURIFIED HUMAN AND HERPES SIMPLEX VIRUS-INDUCED DNA POLYMERASES BY 9-(2-HYDROXYETHOXYMETHYL)GUANINE TRIPHOSPHATE. EFFECTS ON PRIMER-TEMPLATE FUNCTION.

Derse D, Cheng YC, Furman PA, StClair MH, Elion GB
(c/o Cheng) Dept. Pharmacology and Medicine, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
J Biol Chem; 256(22):11447-11451 1981

The inhibition of highly purified herpes simplex virus (HSV)-induced and host cell DNA polymerases by the triphosphate form of 9-(2-hydroxyethoxymethyl)guanine (acyclovir; acycloguanosine) was examined. Acyclovir triphosphate (acyclo-GTP) competitively inhibited the incorporation of dGMP into DNA, catalyzed by HSV DNA polymerase; apparent Km and Ki values of dGTP and acyclo-GTP were 0.15 uM and 0.003 uM, respectively. HeLa DNA polymerase alpha was also competitively inhibited; Km and Ki values of dGTP and acyclo-GTP were 1.2 uM and 0.18 uM, respectively. In contrast, HeLa DNA polymerase beta was insensitive to the analogue. The 'limited' DNA synthesis observed when dGTP was omitted from HSV or alpha DNA polymerase reactions was inhibited by acyclo-GTP in a concentration-dependent manner. Prior incubation of activated DNA, acyclo-GTP, and DNA polymerase (alpha or HSV) resulted in a marked decreased in the utilization of the primer-template in subsequent DNA polymerase reactions. This decreased ability of preincubated primer-templates to support DNA synthesis was dependent on acyclo-GTP, enzyme concentration, and the time of prior incubation. Acyclo-GMP-terminated DNA was found to inhibit HSV DNA polymerase-catalyzed DNA synthesis. Kinetic experiments with variable concentrations of activated DNA and fixed concentrations of acyclo-GMP-terminated DNA polymerase revealed a noncompetitive inhibition of HSV-1 DNA polymerase. The apparent Km of 3'-hydroxyl termini was 1.1 x 10(-7) M, the Kii and Kis of acyclo-GMP termini in activated DNA were 8.8 x 10(-8) M and 2.1 x 10(-9) M, respectively. Finally, 14C-labeled acyclo-GMP residues incorporated into activated DNA by HSV-1 DNA polymerase could not be excised by the polymerase-associated 3',5'-exonuclease activity. (Author abstract) (15 Refs)

45. EFFECTS OF ORAL TREATMENT WITH ACYCLOVIR AND BROMOVINYLDEOXYURIDINE ON THE ESTABLISHMENT AND MAINTENANCE OF LATENT HERPES SIMPLEX VIRUS INFECTION IN MICE.

Field HJ, De Clercq E
Dept. Pathology, Univ. Cambridge, Cambridge, England
J Gen Virol; 56(part2):259-265 1981

Mice infected with herpes simplex virus (HSV) were treated (separately) with the nucleoside analogues acyclovir or bromovinyldeoxyuridine by incorporating the drugs in the drinking water. This method of treatment was found to be effective for both drugs and compared favorably with ip injection. Prompt treatment with either compound could prevent the establishment of latent infections but latent infections once established were intractable using prolonged courses of oral administration. (Author abstract) (23 Refs)

46. INHIBITION OF CELLULAR AND VIRUS-ASSOCIATED NUCLEOTIDE POLYMERASES BY, AND ANTI-HERPES SIMPLEX VIRUS ACTIVITY OF, STREPTOVARICIN DERIVATIVES.

Srivastava BI, DiCioccio RA, Chadha KC, Rinehart KL
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
Antimicrob Agents Chemother; 20(5):653-659 1981

Fourteen streptovaricin derivatives were tested for inhibition of cellular nucleotide polymerases (DNA polymerase alpha, DNA polymerase beta, and DNA polymerase gamma, terminal deoxynucleotidyltransferase [TdT], and RNA polymerase II), simian sarcoma virus deoxyribonucleic acid polymerase, and herpes simplex virus Type 1-induced deoxyribonucleic acid polymerase (HSV-DP). Three compounds (streptovadienal C, prestreptovarone, and streptoval Fc) preferentially inhibited TdT and HSV-DP over the other enzymes. These compounds inhibited HSV-DP more potently than they inhibited TdT. Evidence indicated that the mode of inhibition of TdT and HSV-DP by streptovadienal C and prestreptovarone was by interaction with the enzymes and not with template-primer, initiator, substrates, or divalent cations required for enzyme activity. Furthermore, data suggested that these compounds bind with greater affinity to HSV-DP than to TdT. Streptovadienal C and prestreptovarone were examined for their effect on the replication of herpes simplex virus Type 1 in African green monkey kidney (CV1) cells. These compounds produced 2-and 3-log drops in virus titer, respectively, at concentrations not significantly affecting cell viability. This correlated with evidence indicating a greater binding affinity of these compounds for HSV-DP over cellular nucleotide polymerases. (Author abstract) (27 Refs)

47. DIFFERENTIAL INHIBITION OF HERPES SIMPLEX VIRUSES, TYPE 1 (HSV-1) AND TYPE 2 (HSV-2), BY (E)-5-(2-X-VINYL)-2'-DEOXYURIDINES.

de Clercq E, Verhelst G, Descamps J, Bergstrom DE
Rega Inst. Medical Res., Minderbroedersstraat 10, B-3000 Leuven, Belgium
Acta Microbiol Acad Sci Hung; 28(3):307-312 1981

Antiviral activities of six (E)-5-(2-X-vinyl)-2'-deoxyuridines were tested in primary rabbit kidney cell cultures infected with laboratory strains of herpes simplex virus types 1 and 2. Four of the compounds may be useful as marker tests for rapid and specific diagnosis of human HSV-1 and HSV-2 infections. The tests may be less time-, labor- and reagent-consuming than many previously described typing techniques, including restriction endonuclease mapping. (15 Refs)

48. INTERFERON. TRYING TO LIVE UP TO ITS PRESS.

Hecht A
Public Affairs Dept., FDA Washington, DC
FDA Consum; 15(9):7-9 1981

Research projects on interferon are reviewed, and future possibilities for its use are discussed. Interferon has produced promising results when used against the common cold, herpes zoster, and chicken pox. Initial encouraging results with interferon have been obtained in patients with osteogenic sarcoma, advanced breast cancer, multiple myeloma, and lymphoma. Problems associated with the use of interferon are cost, side-effects, and the difficulties in producing pure samples. (no Refs)

GENERAL REVIEWS

49. GENITAL CANCER AND VIRUSES.

Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

Current data suggesting an association between viruses and genital cancer are reviewed. The main emphasis is on the relationship between herpes simples virus Type 2 (HSV-2) and cervical cancer. Seroepidemiological studies are presented along with emphasis on HSV-transforming and oncogenic potential. Although the evidence is indirect, it is highly suggestive. HSV-2 has the oncogenic potential to produce neoplastic disease in animals. The ability of HSV-2 to transform cells in vitro and for transformed cells to produce tumors in vivo is presently the most direct evidence for oncogenic potential. In vivo experiments, more closely linking HSV-2 and cervical cancer are hampered by the severe cytopathic effect of HSV-2. Evidence associating two other viruses, human cytomegalovirus (CMV) and human papilloma virus (PV), with cervical and prostatic cancer are also discussed. Factors associating CMV with genital cancer include the establishment of persistent infections of the genitourinary tract, transmission by sexual contact, seroepidemiological studies with antibodies and genital cancer, detection of virus particles or virus-specific antigens in genital cancer biopsies, and in vitro transformation studies. Factors associating PV with genital cancer include association with venereal disease, conversion of condylomata acuminata to malignant state, and detection of genital carcinoma within condylomata. (97 Refs)

50. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.

Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

Current evidence on etiology of human cervical neoplasia (CN) was reviewed. Epidemiological factors of possible etiological significance are coitus, marriage, pregnancy, penile factors, syphilis, trichomoniasis, and herpesvirus genitalis (HVG). Seroepidemiologic studies of herpesvirus type 2 (HSV-2) gave indirect evidence of its etiologic role in human CN. Squamous carcinoma of the cervix behaves as a venereal disease. Findings suggest that certain males having venereal diseases may transmit a risk factor for CN by coital contacts. A necessary condition is that certain females are receptive hosts for the putative venereal carcinogen. Risk factor in females is associated with steroid hormone balance (estrogenic hormones). A virion polypeptide AG-4 associated with the active growth phases of CN and a structural component of the HVG, AG-e was identified and isolated. (81 Refs)

51. 'THE HERPESVIRUS HYPOTHESIS' - ARE KOCH'S POSTULATES SATISFIED?

Aurelian L, Manak MM, McKinlay M, Smith CC, Klacsmann KT, Gupta PK
Dept. Comparative Medicine, Johns Hopkins Medical Inst., Baltimore, MD, 21205
Gynecol Oncol; 12(2,part2):S56-S87 1981

The evidence associating herpes simplex virus Type 2 (HSV-2) with squamous cervical carcinoma is critically reviewed.

Thirteen criteria for a causal relationship between a virus and a human cancer are listed and evidence is presented demonstrating that in the case of HSV-2 and cervical cancer these have been fulfilled. The original Koch postulates are discussed from the standpoint of modern concepts of virology. In this context, emphasis is placed on the identification in cervical tumor cells of the viral protein ICP 10/AG-4. This protein is expressed in HSV-2 transformed hamster cells and its expression correlates well with the oncogenic potential of the transformed lines. Consistent with these findings, the expression of ICP 10/AG-4 in cervical cells and the prevalence of the specific antibody that it induces, reflect the progression of the cervical tumor. (Author abstract) (92 Refs)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. TWO LARGE VIRION ENVELOPE GLYCOPROTEINS MEDIATE EPSTEIN-BARR VIRUS BINDING TO RECEPTOR-POSITIVE CELLS.

Wells A, Koide N, Klein G
Brown Univ. Sch. Medicine, Providence, RI, 02912
J Virol; 41(1):286-297 1982

The four major Epstein-Barr virion envelope components were separated by column chromatography and reconstituted into artificial liposomes. These liposomes were tested for their

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ability to bind selectively to Epstein-Barr virus receptor-positive cells. Only when the two high-mol-wt glycoproteins, VE1 and VE2, were present together was a stable binding complex formed. The addition of the other virion envelope components did not increase the levels of binding. This binding was inhibited by unlabeled viable virions and by neutralizing antisera, which recognized the two components. Adsorption of viable virus was also eliminated by the antisera. The enzyme susceptibility pattern of the cell-liposome interaction is similar to that of the virus-cell interaction, thus confirming the specificity of the binding site. A model for Epstein-Barr virus binding in which VE1 and VE2 coordinately recognize the same binding site is presented. (Author abstract) (37 Refs)

2. MULTIMERIC FORMS OF HERPES SIMPLEX VIRUS TYPE 2 GLYCOPROTEINS.

Eberle R, Courtney RJ
(c/o Courtney) Dept. Microbiology, Univ. Tennessee, Knoxville, TN, 37916
J Virol; 41(1):348-351 1982

Herpes simplex virus type 2-specific glycoproteins present in detergent extracts of infected cells were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis under conditions designed to permit detection of multimeric forms of these glycoproteins. Two high-mol-wt glycosylated species were detected when samples were disrupted at lower temperatures or in the absence of any reducing agents. One multimer having an apparent mol wt of 275,000 was identified as a multimer of the gA or gB glycoprotein or both. The second glycoprotein, having a mol wt of approx 230,000, was identified as a multimeric form of the gC glycoprotein. These data indicate that the gC as well as the gA and gB glycoproteins of herpes simplex virus type 2 may exist in a multimeric form. (Author abstract) (13 Refs)

3. SIMILARITIES AND DIFFERENCES IN THE FC-BINDING GLYCOPROTEIN (GE) OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 AND TENTATIVE MAPPING OF THE VIRAL GENE FOR THIS GLYCOPROTEIN.

Para MF, Goldstein L, Spear PG
Dept. Medicine, Ohio State Univ. Coll. Medicine, Columbus, OH, 43210
J Virol; 41(1):137-144 1982

We performed affinity chromatography and immunoprecipitation experiments to determine whether cells infected with herpes simplex virus type 2 (HSV-2) expressed a glycoprotein that was functionally and antigenically related to the HSV-1 Fc-binding glycoprotein designated gE. We found that a protein from extracts of HSV-2-infected HEp-2 cells bound specifically to an Fc affinity column and that the electrophoretic mobility of this protein in sodium dodecyl sulfate-acrylamide gels was slightly less than the mobility of HSV-1 gE. Immunoprecipitation experiments performed with an antiserum prepared against HSV-1 gE revealed that (i) extracts from HSV-2-infected cells contained a glycoprotein that was antigenically related to HSV-1 gE; (ii) the electrophoretic mobility of the HSV-2 gE was indistinguishable from the mobility of the HSV-2 Fc-binding protein; (iii) the antiserum reacted with both newly synthesized transient forms and stable fully processed forms of both HSV-1 gE and HSV-2 gE; and (iv) the transient and stable forms of HSV-2 gE all had lower electrophoretic mobilities than their HSV-1 counterparts. Electrophoretic analyses of gE precipitated from extracts of HEp-2 cells infected with two sets of HSV-1 x HSV-2 intertypic recombinant viruses suggested that the gene for gE is located at the right end of the HSV genome (0.85 to 0.97 map units) in the unique portion of the S component. (Author abstract) (20 Refs)

4. OLIGOPEPTIDE ANALYSIS OF HEXONS OF HUMAN ADENOVIRUSES TYPE 1, 2, AND 6 AND OF SIMIAN ADENOVIRUS SA7.

Tarasishin LA, Khil'ko SN, Diachenko NS, Naroditskii BS, Tikhonenko TI, Vantsak NP, Kovalishin GG, Dreizin RS, Loparev VN
D. K. Zabolotnyi Inst. Microbiology and Virology, Kiev, USSR
Vopr Virusol; (5):574-581 1981

Oligopeptide mapping of structural and soluble hexons of human adenoviruses type 1, 2, and 6 and of simian adenovirus SA7 showed the presence of common and unique peptide sequences. (20 Refs) (In RUS)

5. STRUCTURAL HOMOLOGY OF THE MAJOR INTERNAL PROTEINS OF ENDOGENOUS TYPE C VIRUSES OF TWO DISTANTLY RELATED SPECIES OF OLD WORLD MONKEYS: MACACA ARCTOIDES AND COLOBUS POLYKOMOS.

Oroszlan S, Copeland TD, Gilden RV, Todaro GJ
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Virology; 115(2):262-271 1981

The major internal protein (p30) of MAC-1, an endogenous Type C virus of Macaca arctoides and the p30 of CPC-1, an endogenous Type C virus of Colobus polykomos were purified and subjected to primary structure analysis. Despite the distant evolutionary relationship (approx 20 Myr) between these two species of Old World monkeys, the amino acid compositions of the viral p30s were very similar and their COOH-terminal sequences (5 residues) were found to be identical. Moreover, the NH2-terminal sequences (up to 36 residues) differed only in three positions. Both the NH2-and COOH-terminal sequences showed extensive homology to respective sequences of p30s of known Type C viruses from other mammalian species. Statistical analysis of the sequence relatedness revealed that MAC-1 and CPC-1 p30s are not more closely related to the p30s of another family of endogenous primate viruses isolated from baboons (Papio genus) than they are to p30s of those viruses isolated from lower mammals. On the basis of these p30 sequence relationships MAC-1 and CPC-1 together with MMC-1, an endogenous virus of Macaca mulatta, can be classified into a new (4th) subgroup. Avian reticuloendotheliosis virus and its relatives, transforming viruses of birds are more related to this primate virus subgroup than to any of the three other subgroups of mammalian Type C viruses. (Author abstract) (33 Refs)

6. TYPE C VIRUS PARTICLES IN A CORD T-CELL LINE DERIVED BY CO-CULTIVATING NORMAL CO RD LEUKOCYTES AND HUMAN LEUKAEMIC T CELLS.

Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, Nagata K, Hinuma Y
Dept. Medicine, Kochi Medical Sch., Kochi 781-51, Japan
Nature; 294(5843):770-771 1981

Cocultivation of adult T-cell leukemia (ATL) cells with cord WBC from a male infant was used to establish a T-cell line that expresses ATL-associated antigens (ATLAs) and contains numerous C-type virus particles. The ATLAs were detected by indirect immunofluorescence using ATL patients' sera and fluorescein isothiocyanate-conjugated goat antihuman IgG. Thin-section electron microscopy revealed the virus particles, which are predominantly mature and consist of an electron-dense nucleoid and an outer membrane. (8 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

7. THE RELATIONSHIP BETWEEN TUMOR PROMOTER BINDING AND EPSTEIN-BARR VIRUS INDUCTION IN HUMAN LYMPHOBLASTOID CELL LINES.

Yamamoto N, Bauer G
Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Str. 11, 7800 Freiburg, W. Germany
J Cell Physiol; 109(3):397-402 1981

Epstein-Barr virus (EBV) nonproducer Raji, and its derivative NC-37 cells, were incubated with 3H-TPA (12-O-tetradecanoyl-phorbol-13-acetate), and cell associated radioactivity determined. TPA dissociation was studied by centrifuging previously incubated cells, and resuspending them in fresh medium to the original concentration. Free and bound 3H-TPA were measured radiometrically. Serum components alone can bind TPA within 60 min, but cells can complete for part of this TPA. Binding of TPA to cells is temperature dependent; absence of serum approx doubles the rate of TPA binding. Dissociation of TPA from cells is rapid, and is greater in the presence of serum. (24 Refs)

8. EPSTEIN-BARR VIRUS-INDUCED EARLY POLYPEPTIDES IN RAJI AND NC37 CELLS ACTIVATED BY DITERPENE ESTER TPA IN COMBINATION WITH N-BUTYRATE.

Kawanishi M, Sugawara K, Ito Y
(c/o Ito) Dept. Microbiology, Kyoto Univ., Kyoto 606, Japan
Virology; 115(2):406-409 1981

Epstein-Barr virus (EBV)-induced early polypeptides in activated nonproducer Raji and NC37 cells, and such polypeptides induced in producer P3HR-1 cells were studied for comparison. The major difference was that the two polypeptides with molecular weights of 140,000 (140K) and 120,000 (120K) which are presumably involved in viral DNA synthesis in the activated producer cells, were not detectable in the activated nonproducer cells. (Author abstract) (20 Refs)

9. CHARACTERIZATION OF HUMAN CELLS PERSISTENTLY INFECTED WITH CYTOMEGALOVIRUS AND EXPOSED TO A CHEMICAL CARCINOGEN.

Li JL, Albrecht T
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Int J Cancer; 29(1):49-55 1982

A non-productive, persistent human cytomegalovirus (CMV) infection was developed in human embryo lung (LU) cells by initially using supraoptimal temperatures to restrict the replication of a recent CMV isolate (76-24). Although CMV replication was observed in some cells within a few wk of shifting the cultures to 37 C and subculturing, CMV cytopathic effects and infectious CMV were not detected with further subculturing during the next 5 wk. CMV-specific nuclear antigens were, however, observed in most cells (designated LU-76-24) for 38 additional culture passages made during the following 12 mo. Although the LU-76-24 cells were morphologically distinct from LU cell cultures carried in parallel as controls, the LU-76-24 were contact-inhibited in spite of a somewhat disoriented growth pattern. Treatment of LU-76-24 cells with 0.05 ug/ml of the chemical carcinogen 4-nitroquinoline 1-oxide (NQO) induced a lytic CMV infection from which a clone of cells (designated LUC-NQO) was isolated. No effect was seen when LU cells were treated with the same dose of NQO. LUC-NQO cells were morphologically altered from LU-76-24 cells and had lost contact inhibition. Even though CMV-specific nuclear antigens were observed in LUC-NQO cells, infectious CMV was not detected in lysates of these cells, nor was CMV rescued by co-cultivation of these cells with susceptible cells or by induction with 5-iodo-2'-deoxyuridine. LUC-NQO, but not LU or LU-76-24 cells, plated with good efficiency in semi-solid medium. The results indicate that long-term, non-productive, persistent CMV infections can be established in vitro and suggest that such cells may be more susceptible than non-infected cells to the action of chemical carcinogens. (Author abstract) (37 Refs)

10. TRANSFORMATION BY ADENOVIRUS EARLY REGION 2A TEMPERATURE-SENSITIVE MUTANTS AND THEIR REVERTANTS.

Logan J, Nicolas JC, Topp WC, Girard M, Shenk T, Levine AJ
Dept. Microbiology, State Univ. New York, Sch. Medicine, Stony Brook, NY, 11794
Virology; 115(2):419-422 1981

H5ts107 is a temperature-sensitive (ts) mutant of adenovirus Type 5 whose alteration maps in the structural gene for the viral DNA binding protein. Temperature-independent revertants of this mutant that form plaques at 39 C in HeLa cells have been isolated. These revertants fall into two classes: (1) ts+ revertants for growth and plaque formation at 39 C in both HeLa cells and 293 cells, a human cell line transformed by Type 5 adenovirus; (2) ts+ for growth and plaque formation at 39 C in HeLa cells, but ts for growth and plaque formation in 293 cells. The frequency of rat cell transformation by H5ts107 was fivefold higher than that of wild-type adenovirus. A Class 1 revertant, r(st107)127, transformed cells at the wild-type virus frequency while a Class 2 revertant, r(ts107)202, retained the ability to transform cells at the higher frequency. When the XhoI-C DNA fragment from these viruses, which contains the left end 15.5% of the viral genome, was employed to transform rat cells, then Ad5 wt, H5ts107, r(ts107)127, and r(ts107)202 DNAs all transformed with approximately equal frequencies. (Author abstract) (17 Refs)

11. VIRAL MESSENGER RNAS IN SIX LINES OF ADENOVIRUS-TRANSFORMED CELLS.

Lewis JB, Mathews MB
(c/o Mathews), Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11724
Virology; 115(2):345-360 1981

We have compared the proteins translated in vitro using virus-specific mRNA from six lines of adenovirus-transformed cells (F4, F17, F19, REM, T2C4, and 293) with those made using RNA from productively infected cells. The mRNAs for proteins E1A-58K, 54K, 48K, and 42K, and for E1B-15K, were detected in all cell lines and for E1B-57K in at least five of the lines. Neither of the minor E1A mRNAs (for proteins 25K and 28K) found under specific conditions in infected cells were found in any transformed cell line. Two cell lines, F4 and T2C4, contained small amounts of other mRNAs encoded within region E1B including in the latter case one not detected in infected cells. The lines F4, REM, and T2C4 contain at least some E4 mRNAs, again including in the latter case one not detected in infected cells. T2C4 cells also contain E3 mRNAs, E2A-72K protein mRNA, and two E2B mRNAs, although the 32B proteins are not identical to any found in infected cells. The F19 and T2C4 lines express mRNAs encoded between 11 and 17 map units, the 'IVa2 region', but do not include the mRNA for polypeptide IVa2 itself. Some early mRNAs, including the 'immediate early' mRNAs, have not been detected in any of these lines of transformed cells: nor did the cell lines contain any mRNAs found exclusively at late times during productive infection. Comparison of these results with the properties of the cells tentatively suggest a correlation (although not necessarily causal) between the expression of additional viral genes and increased tumorigenicity. (Author abstract) (58 Refs)

12. RECENT DISCOVERIES ON CELLULAR PROTEINS IN RELATION TO VIRALLY AND CHEMICALLY INDUCED CARCINOGENESIS.

Jornvall H

Kemiska Institutionen I, Karolinska Institutet, S-104 01 Stockholm, Sweden

Lakartidningen; 78(41):3585-3586 1981

Recent studies on the molecular mechanisms of carcinogenesis suggest the existence of a cellular protein ('53K') common to virally and chemically induced cell transformations. This type of protein binds some T-antigens from oncogenic DNA viruses, including large T-antigen from SV40 and Epstein-Barr virus-determined nuclear antigen. Transformation-related proteins from oncogenic RNA viruses are similar to normal cellular proteins. Several of these proteins have phosphorylating activity, and some of them have been found to be protein kinases. Associations of such proteins with the plasma membrane have also been shown. These different connections between various tumor-related proteins and normal cellular proteins suggest the importance of gene determination in transformations. (11 Refs) (In SWE)

13. SIMILARITIES AND DIFFERENCES BETWEEN THE EFFECTS OF EPIDERMAL GROWTH FACTOR AND ROUS SARCOMA VIRUS.

Cooper JA, Hunter T

Tumor Virology Lab., Salk Inst., San Diego, CA, 92138

J Cell Biol; 91(3):878-883 1981

We have derived a line of A431 human tumor cells infected with Rous sarcoma virus (RSV). The infected cells contain the RSV-transforming protein, pp60src, which has characteristic tyrosine-specific protein kinase activity. As in other RSV-transformed cells, a 36,000-dalton protein is phosphorylated in RSV-infected A431 cells. Addition of epidermal growth factor (EGF) to the cells induces further phosphorylation of this protein. In contrast, this phosphoprotein is not detected in uninfected A431 cells, except when treated with EGF. Increased phosphorylation of the EGF receptor protein and of an 81,000-dalton cellular protein is dependent upon addition of EGF to the culture fluids, in both control and RSV-infected A431 cells. The results are discussed with reference to the similarities and differences between the tyrosine-specific protein kinases induced by RSV and activated by EGF. (Author abstract) (42 Refs)

14. TRANSFORMATION OF NORMAL HUMAN CORD LYMPHOCYTES BY CO-CULTIVATION WITH A LETHALLY IRRADIATED HUMAN T-CELL LINE CARRYING TYPE C VIRUS PARTICLES.

Miyoshi I, Yoshimoto S, Taguchi H, Ohtsuki Y, Kubonishi I, Shiraishi Y, Akagi T
Dept. Anataomy, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan
Gan; 72(6):997-998 1981

Normal human cord WBC were co-cultured with lethally irradiated MT-2 cells to produce a T-cell line of cord WBC origin which harbored type C virus particles and adult T-cell leukemia-associated antigens (ATLA). On the 11th day of culture, 1 x 10(6) lethally x-irradiated (6,000 R) MT-2 cells were added to two of four dishes of cord WBC. Control cultures included two dishes of irradiated MT-2 cells without cord WBC and two dishes of cord WBC alone. All cultures were incubated at 37 C in a humidified 7.5% CO2 atmosphere. Two wk after co-culture, scattered foci of cell aggregates were observed on the sheets of macrophages. Continuous growth of cells developed in two of the co-cultured dishes, and this cell line, designated Ok, was maintained in culture for 3 mo. The Ok line consisted of mostly immature lymphoid cells with multinucleate giant cells. Sixty-six percent of the Ok cells formed spontaneous rosettes with neuraminidase-treated sheep RBC. Most of the Ok cells were positive for Leu-1 and OK11, but negative for Leu-2a and Leu-3a. None of the 145 Ok cells studied contained a Y chromosome; 41/46 cells had a 46,XX karyotype. Electron microscopy revealed many type C virus particles in the extracellular spaces. Most of the Ok cells were positive for ATLA when reacted with ATL patient's sera. The cultured cells gave a positive reaction with five sera from ATL patients but not with five sera from normal control individuals. These findings suggest that the type C virus was apparently transmitted from the MT-2 cells to the cord lymphocytes during co-cultivation. (8 Refs)

VIRUS REPLICATION AND EXPRESSION

15. EPSTEIN-BARR VIRUS-INDUCED DEOXYNUCLEASE AND THE REUTILIZATION OF HOST-CELL DNA DEGRADATION PRODUCTS IN VIRAL DNA REPLICATION.

Feighny RJ, Henry BE, Pagano JS
Cancer Res. Center, Univ. North Carolina, Sch. Medicine, Chapel Hill, NC, 27514
Virology; 115(2):395-400 1981

Extracts of Raji cells superinfected with EBV obtained from P3HR-1 producer cells revealed the presence of a DNase activity. Template specificity determinations disclosed exonuclease activity on both single-stranded and double-stranded molecules. The activity could be abolished by EBV antiserum. The DNase activity was detectable 18 hr after superinfection. A possible function for the enzyme was suggested by experiments in which radiolabel, which was initially present only at the density of cellular DNA, was chased into DNA banding at the density of EBV DNA. The chase of incorporated label was first observed 36 hr after superinfection and accounted for 10% of the total label present in both DNA peaks. The gradual shift of label reached a maximum of 20% of the total label by 72 hr after infection. Rate-velocity centrifugation analyses revealed that cellular DNA was degraded after superinfection.

The use of DNA synthesis inhibitors suggested that the host-cell DNA degradation products were recycled into nascent EBV DNA via the cellular salvage pathway. (Author abstract) (15 Refs)

16. EXPRESSION OF EPSTEIN-BARR VIRAL EARLY ANTIGEN IN MONOLAYER TISSUE CULTURES AFTER TRANSFECTION WITH VIRAL DNA AND DNA FRAGMENTS.

Grogan E, Miller G, Henle W, Rabson M, Shedd D, Niederman JC
Dept. Pediatrics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Virol; 40(3):861-869 1981

Antigens associated with the Epstein-Barr virus (EBV) replicative cycle were found in the nucleus and cytoplasm of human placental, Vero, BSC-1, and owl monkey kidney cells transfected with EBV DNA prepared from several different strains of virus. The number of antigen-positive nuclei increased when transfection was followed by cell fusion induced by inactivated Sendai virus. About 1,200 antigen-positive foci were induced per ug of EBV DNA. On the basis of their reactivity with various well-characterized human sera, it appears that the antigens are part of the early antigen complex. None of the four restrictive endonucleases, EcoRI, HindIII, SalI, and BamHI, destroyed the ability of EBV DNA to induce early antigen. However, only SalI seemed to leave intact the full spectrum of antigen expression by the HR-1 and FF41 strains of EBV DNA. By means of transfection with recombinant DNA plasmids containing different EBV (FF41) DNA fragments generated by EcoRI, we showed that the coding region for early antigen was at least partially contained on the 17.2-megadalton EcoRI B fragment. (Author abstract) (22 Refs)

17. EPSTEIN-BARR VIRUS-RELATED DNA-BINDING PROTEINS INDUCED BY N-BUTYRATE IN P3HR-1 CELLS.

Sugawara K, Kawanishi M, Ito Y
(c/o Ito) Dept. Microbiology, Kyoto Univ., Kyoto 606, Japan
Virology; 116(1):354-358 1982

Epstein-Barr virus (EBV)-related early and late proteins induced in P3HR-1 cells by n-butyrate treatment were examined for DNA-binding ability using affinity chromatography on native and denatured DNA-cellulose. At least 5 (140K, 120K, 50K, 40K and 35K) of 16 early polypeptides and 3 (145K, 46K and 18K) of 6 late polypeptides were identified as DNA-binding proteins, and most of them bound to both native and denatured DNA. The results indicate that EBV-induced products contain proteins involved in viral DNA replication and in encapsidation. (Author abstract) (28 Refs)

18. INCORPORATION INTO DNA OF THE BASE ANALOG 2-AMINOPURINE BY THE EPSTEIN-BARR VIRUS-INDUCED DNA POLYMERASE IN VIVO AND IN VITRO.

Grossberger D, Clough W
Dept. Biochemistry and Molecular Biology, Harvard Univ., 7 Divinity Ave., Cambridge, MA, 02138
Proc Natl Acad Sci USA; 78(12):7271-7275 1981

The Epstein-Barr virus (EBV)-induced intracellular DNA polymerase was assayed in vitro for the ability to utilize the mutagenic nucleotide analog 2-aminopurine deoxyribose triphosphate (d2apTP), incorporating it as the corresponding monophosphate into DNA or poly[d(A-T)] template. Bacteriophage T4, lymphocyte alpha, and the EBV particle-associated DNA polymerases were assayed simultaneously for direct comparison. Unlike these three polymerases, which were capable of distinguishing between d2apTP and dATP with a strong preference for the latter, the EBV-induced DNA polymerase only weakly distinguished between dATP and d2apTP and incorporated substantial amounts of d2apTP into template. Detergent-treated lymphocyte nuclei undergoing a high level of EBV DNA synthesis were shown to incorporate the 2-aminopurine analog of dATP into viral DNA. The relative inability of the EBV-induced DNA polymerase to distinguish between the two purine nucleotides reported here is consistent with previous reports on the ready incorporation of other nucleotide analogs into DNA polymerases induced by other herpesviruses. Because most antiherpes agents currently in use or under study are nucleotide analogs, the viral mutagenic properties of these drugs should be examined. (Author abstract) (41 Refs)

19. INDUCTION OF EPSTEIN-BARR VIRUS EARLY ANTIGENS BY INTERCALATING CHEMICALS IN B95 -8 CELLS.

Yamamoto N, Zur Hausen H
(c/o zur Hausen) Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Virology; 115(2):390-394 1981

Various intercalating chemicals, such as ethidium bromide (ETB), proflavin (PF), acridine orange (AO), actinomycin D (AMD), methyl green (MG), Hoechst dye (HD), and trioxsalen (TX), have been tested for their effect on the induction of Epstein-Barr virus (EBV) antigens in several lymphoblastoid cell lines. ETB, PF, AO, and AMD enhanced induction of early antigens (EA) in B95-8 cells 3-to 10-fold. In contrast, viral capsid antigen (VCA) synthesis was not significantly affected by this treatment. Besides B95-8 cells only cells of the M-ABA line were induced to EA synthesis though to a lesser extent. All other cell lines tested did not respond to intercalating chemicals. Simultaneous treatment of B95-8 cells with ETB and 13-cis-retinoic acid inhibits the EA induction efficiently. ETB 'superinduced' EA neither in 12-O-tetradecanoyl-phorbol-12-acetate (TPA)- nor in iododeoxyuridine (IUdR)-treated B95-8 cells. (Author abstract) (29 Refs)

20. CHARACTERIZATION OF HERPES SIMPLEX VIRUS PERSISTANCE IN A HUMAN T LYMPHOBLASTOID CELL LINE.

Cummings PJ, Lakomy RJ, Rinaldo CR
Dept. Allied Health, Youngstown State Univ., Youngstown, OH, 44555
Infect Immun; 34(3):817-827 1981

Persistent, dynamic-state infection with herpes simplex virus (HSV) Type 1 has been maintained in human T Lymphoblastoid (CEM) cells for many mo after initial infection with the wild-type virus (HSV0) (input virus/cell multiplicity of 1.0). Persistently infected cells grew as well as uninfected cells, except during occasional periods of crisis (increased viral replication and cytopathic effect). Cells could survive the crisis when they were maintained for twice the usual time interval (8 to 10 rather than 4 to 5 days) before subculture. Interferon was not detectable in the cultures. HSV0 was compared with HSVp1, a small plaque-forming isolate from persistently infected CEM cells. Primary infection of CEM cells with HSV0 at a low input multiplicity (0.01) led to abortive replication, whereas infection with HSVp1 at the same multiplicity resulted in either rapidly lytic or persistent infection depending upon the time interval of subculture. Approximately 55% of plaque-purified clones of HSVp1, as compared with only 5% of HSV0 clones, displayed temperature-sensitive growth in Vero cells. Defective interfering virus was not detectable in uncloned HSVp1 by interference assay. Persistently infected cultures 'cured' by treatment with HSV antiserum or incubation at 39 C were resistant to reinfection with HSV but permissive for vesicular stomatitis virus replication, suggesting that these treatments modulated a shift from the dynamic -state to the static-state, latent infection. These studies provide a model for characterization of HSV persistence and latency in a highly differentiated human cell line. (Author abstract) (40 Refs)

21. RESISTANCE OF NEONATAL HUMAN LYMPHOID CELLS TO INFECTION BY HERPES SIMPLEX VIRUS OVERCOME BY AGING CELLS IN CULTURE.

Grogan E, Miller G, Moore T, Robinson J, Wright J

(c/o Miller) Dept. Pediatrics, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510

J Infect Dis; 144(6):547-556 1981

Mononuclear leukocytes freshly harvested from human umbilical cord blood were refractory to infection by herpes simplex virus (HSV) Type 1, whereas cells aged in vitro for a wk produced 10-to 100-fold or greater more virus. Increased sensitivity of aged cells to infection by HSV was not dependent on active DNA synthesis by the cells at the time of exposure to HSV. The aging phenomenon was not due to the outgrowth of a specific cell subpopulation that is uniquely susceptible to HSV because increased sensitivity to HSV Type 1 occurred in a variety of cell subpopulations enriched or depleted of T lymphocytes, phagocytic cells, or adherent cells. About 25% of aged cells contained virions detectable by electron microscopy, considerably more cells than formed infectious centers. These virions were seen in large activated lymphocytes which are the principal cell subpopulation present in the aged cultures, but virions were also seen in small lymphocytes. (Author abstract) (21 Refs)

22. A CASCADE OF ADENOVIRUS EARLY FUNCTIONS IS REQUIRED FOR EXPRESSION OF ADENO-ASSOCIATED VIRUS.

Richardson WD, Westphal H

Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205

Cell; 27(1,part2):133-141 1981

One measurable biological activity of early adenovirus genes is their ability to promote growth of the defective adeno-associated virus, AAV. We have identified an ordered sequence of communications among the early genes of adenovirus Type 2 (Ad2) that results in expression of the helper activity. We purified DNA fragments and mRNAs corresponding to early Ad2 regions E1, E2A, E3 and E4 and injected them via glass capillaries into AAV-infected cells. DNAs were placed in the nucleus, mRNAs in the cytoplasm. AAV DNA and proteins synthesized in response to the injected Ad2 nucleic acids were extracted from as few as 100 cells and identified by gel electrophoresis. Our results reveal a cascade of early Ad2 gene regulation, E1 to E2A to E4, with E4 providing the helper effect for AAV. (Author abstract) (51 Refs)

23. IN VITRO TRANSCRIPTION OF ADENOVIRUS.

Fire A, Baker CC, Manley JL, Ziff EB, Sharp PA

Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139

J Virol; 40(3):703-719 1981

A series of recombinants of adenovirus DNA fragments and pBR322 was used to test the transcriptional activity of the nine known adenovirus promoters in a cell-free extract. Specific initiation was seen at all five early promoters as well as at the major late promoter and at the intermediate promoter for polypeptide IX. The system failed to recognize the two other adenovirus promoters, which were prominent in vivo only at intermediate and late stages in infection. Microheterogeneity of 5' termini at several adenovirus promoters, previously shown in vivo, was produced in the in vitro reaction and indeed appeared to result from heterogeneous initiation rather than 5' processing. To test for the presence of soluble factors involved in regulation of mRNA synthesis, the activity of extracts prepared from early and late stages of infection was compared on an assortment of viral promoter sites. Although mock and early extracts showed identical transcription patterns, extracts prepared from late stages gave 5-to 10-fold relative enhancement of the late and polypeptide IX promoters as compared with early promoters. (Author abstract) (43 Refs)

24. INITIATION OF ADENOVIRUS DNA REPLICATION: DETECTION OF COVALENT COMPLEXES BETWEEN NUCLEOTIDE AND THE 80-KILODALTON TERMINAL PROTEIN.

Challberg MD, Ostrove JM, Kelly TJ

Dept. Molecular Biology and Genetics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205

J Virol; 41(1):265-270 1982

We have previously shown that the 5'-terminal deoxycytidine residue of each nascent adenovirus 5 DNA strand synthesized in vitro is covalently linked to the 80-kilodalton (kd) terminal protein precursor via a phosphodiester bond to a serine residue in the protein. When extracts prepared from adenovirus 5-infected cells are incubated with [alpha-32P]dCTP as the only added deoxynucleoside triphosphate, complexes consisting of nucleotide covalently linked to the 80-kd protein can be detected. The nucleotide moieties present in such complexes include d(pC) and d(pCpA), the 5'-terminal nucleotide and dinucleotide of adenovirus 5 DNA, respectively, as well as some longer oligonucleotides. The formation of these complexes requires the presence of adenovirus DNA containing the attached 55-kd terminal protein and ATP. Extracts from H5ts125-infected cells which are defective in DNA replication catalyze complex formation to the same extent as adenovirus-coded 72-kd DNA-binding protein is apparently not required. Most, if not all, of the 80-kd protein-nucleotide complexes that are formed are noncovalently bound to the input viral DNA. These observations are consistent with the protein-priming model for the initiation of adenovirus DNA replication. (Author abstract) (25 Refs)

25. SPECIFIC IN VITRO INITIATION OF TRANSCRIPTION ON THE ADENOVIRUS TYPE 2 EARLY AND LATE EII TRANSCRIPTION UNITS.

Mathis DJ, Elkaim R, Kedinger C, Sassone-Corsi P, Chambon P
(c/o Chambon), Institut de Chimie Biologique, Strasbourg 67085, Cedex, France
Proc Natl Acad Sci USA; 78(12):7383-7387 1981

Three transcription units are present in the adenovirus Type 2 region EII. Transcription units EIIaE and EIIaL encode the mRNA for the 72,000-dalton DNA binding protein, early and late in the lytic cycle, respectively, and transcription unit EIIb encodes the mRNA for the protein that binds to the 5' termini of adenovirus DNA. By using a cell-free transcription system in the presence of purified RNA polymerase B (or II), we have obtained specific initiation of transcription from both the EIIaE promoter, which does not contain a T-A-T-A box, and the EIIaL promoter, which does. In addition, we have identified a new EII T-A-T-A box promoter that is located close to the early non-T-A-T-A box promoter and is used both in vivo and in vitro. (Author abstract) (28 Refs)

26. EFFICIENT INFECTION OF MONKEY CELLS WITH DNA OF SIMIAN VIRUS 40.

Sompayrac LM, Danna KJ
(c/o Danna) Dept. Molecular, Cellular and Development Biology, Univ. Colorado, Boulder, CO, 80309
Proc Natl Acad Sci USA; 78(12):7575-7578 1981

With standard protocols for DNA infection, only a small fraction (about 4%) of monkey cells exposed to purified DNA of simian virus 40 (SV40) exhibits signs of infection. We have devised a protocol by which we can extend the time of exposure of BSC-1 cells to DNA in the presence of low concentrations of DEAE-dextran. The efficiency of infection is proportional to the time of exposure. With an 8-hr exposure, we are reproducibly able to infect 25% of the cells, and we have been able to achieve levels of infection as high as 50% with a 16-hr exposure. The percentage of cells infected was measured either by scoring for nuclei positive for SV40 tumor antigen or by an infectious centers assay. We also report the use of ethidium bromide as a nonspecific nuclear counterstain in the immunofluorescence assay for SV40 tumor antigen. (Author abstract) (7 Refs)

27. T ANTIGEN REPRESSION OF SV40 EARLY TRANSCRIPTION FROM TWO PROMOTERS.

Hansen U, Tenen DG, Livingston DM, Sharp PA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 27(3):603-612 1981

The SV40 early mRNAs encode large (T) and small (t) tumor antigens. During the lytic cycle, the 5' termini of the early mRNAs undergo a shift: shortly after infection only an initiation site downstream from the TATA box is utilized; later an upstream initiation site becomes prominent. Both initiation sites are utilized in an in vitro transcription extract. D2T, a T antigen analog, specifically represses transcription in vitro from both initiation sites, but at different concentrations. Binding of D2T to Site I suppresses initiation from the site downstream of the TATA box; binding to Sites II and I suppresses initiation from the upstream site. The role of T antigen binding in repression of transcription and in the shift of initiation sites on the early strand is discussed. (Author abstract) (52 Refs)

28. PREREPLICATIVE EVENTS INVOLVING SIMIAN VIRUS 40 DNA IN PERMISSIVE CELLS.

Rinaldy A, Feunteun J, Rosenberg BH
(c/o Rosenberg) Walker Lab., Sloan-Kettering Inst., Rye, NY, 10580
J Virol; 41(1):237-243 1982

Simian virus 40 DNA molecules were found to be unable to replicate for 9 hr after infection, even in cells that were already replicating the DNA of preinfecting simian virus 40; after 9 hr, the ability of the DNA to replicate began to rise sharply. The kinetics of activation indicated that each DNA molecule undergoes a series of slow consecutive reactions, not involving T-antigen, before it can replicate. These pre-replicative molecular transformations probably involve configurational changes; their nature and their relation to the initiation of viral DNA synthesis is discussed. Observation of the replicative behavior of one viral DNA in the presence of another was made possible by the use of two different mutants with distinguishable DNAs: a viable deletion mutant containing DNA insensitive to TaqI restriction enzyme was used to provide viral functions required for replication, and a tsA mutant with TaqI-sensitive DNA was introduced at various times as a probe to determine the ability of the DNA to replicate under different conditions. (Author abstract) (20 Refs)

29. MAPPING THE IN VIVO ARRANGEMENT OF NUCLEOSOMES ON SIMIAN VIRUS 40 CHROMATIN BY THE PHOTOADDITION OF RADIOACTIVE HYDROXYMETHYLTRIMETHYLPSORALEN.

Robinson GW, Hallick LM
Dept. Biochemistry, Oregon Health Sciences Univ., Portland, OR, 97201
J Virol; 41(1):78-87 1982

Intracellular simian virus 40 (SV40) chromatin was photoreacted with a 3H-labeled psoralen derivative, hydroxymethyltrimethylpsoralen (HMT), at 48 hr postinfection. Psoralen compounds have been shown to readily penetrate intact cells and, in the presence of long-wavelength UV light, form covalent adducts to DNA, preferentially at regions unprotected by nucleosomes. The average distribution pattern of [3H]HMT on the SV40 genome was determined by specific activity measurements of the DNA fragments generated by HindIII plus HpaII or by AluI restriction enzyme digestion. At levels of 1 to 10 [3H]HMT photoadducts per SV40 molecule, the radiolabel was found to be distributed nonrandomly. Comparison of the labeling pattern in vivo with that of purified SV40 DNA labeled in vitro revealed one major difference. A region of approx 400 base pairs, located between 0.65 and 0.73 on the physical map, was preferentially labeled under in vivo conditions. This finding strongly suggests that the highly accessible region near the origin of replication, previously observed on isolated SV40 'minichromosomes,' exists on SV40 chromatin in vivo during a lytic infection. (Author abstract) (66 Refs)

30. ULTRAVIOLET IRRADIATION INHIBITS ENCAPSIDATION OF SIMIAN VIRUS 40 CHROMATIN.

Roman A, Edenberg HJ
Dept. Microbiology and Immunology, Indiana Univ. Sch. Medicine, Indianapolis, IN, 46223
J Virol; 40(3):729-734 1981

During normal maturation the majority of pulse-labeled simian virus 40 DNA progresses from chromatin to previrions and virions within 5 hr. UV light inhibits this progression. In heavily irradiated culture (108 J m(-2)) most of the simian virus 40 DNA synthesized immediately before irradiation remains as chromatin for at least 5 hr. This inhibition of maturation seems to be a result of the inhibition of protein synthesis. The data suggest that the pool of proteins required for maturation is sufficient to convert one-third of the simian virus 40 DNA molecules labeled in a 10-min pulse (at 33 hr postinfection) from chromatin to previrions and virions and is exhausted within 1 hr. (Author abstract) (26 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

31. CLONING OVERLAPPING DNA FRAGMENTS FROM THE B95-8 STRAIN OF EPSTEIN-BARR VIRUS REVEALS A SITE OF HOMOLOGY TO THE INTERNAL REPETITION.

Buell GN, Reisman D, Kintner C, Crouse G, Sugden B
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Virol; 40(3):977-982 1981

Overlapping, sheared DNA fragments from the B95-8 strain of Epstein-Barr virus were cloned in Charon 4A. Eleven recombinant phages plus one recombinant plasmid contained all of the sequences found in B95-8 virion DNA. Analysis of recombinant DNA molecules revealed a previously undetected site of homology to the internal repetition found in Epstein-Barr virus DNA. This site was adjacent to or at a site which was unstable when the recombinant DNA was propagated as phage DNA in prokaryotic hosts. (Author abstract) (14 Refs)

32. THE EFFECT OF A TEMPERATURE-SENSITIVE LESION IN THE ALKALINE DNASE OF HERPES SIMPLEX VIRUS TYPE 2 ON THE SYNTHESIS OF VIRAL DNA.

Francke B, Garrett B
Dept. Human Genetics, Yale Univ. Medical Sch., 333 Cedar St., New Haven, CT, 06510
Virology; 116(1):116-127 1982

The alkaline DNase of herpes simplex virus Type 2 appears to be a nonessential function, since revertants of the original ts13 mutant selected for growth at nonpermissive temperature, have reverted only in the thermostability of the virus particle while still inducing a temperature-sensitive DNase. The properties of one revertant, 4-8, are investigated in this report. During infection at 38.5 C production of infectious virus is reduced ca 10-fold and 4-8 forms tiny plaques on monolayers when compared to 31.5 C or to wild type virus at either temperature, where normal plaque sizes are observed. 4-8 is DNA+ /- at 38.5 C, producing 5 to 10% of the viral DNA made at 31.5 C or by wild type virus at either temperature, similar to the DNA phenotype of the original ts13. DNase activity is absent from 4-8 infected cells at 38.5 C and DNA polymerase levels are reduced four- to five-fold. Although the viral DNA polymerase, when assayed in extracts from cells infected at 31.5 C is more heat stable in 4-8 than in wild type, the DNA polymerase induced by 4-8 at 31.5 C is temperature sensitive in vivo, when infected cells are shifted from 31.5 C to 38.5 C. The drop in DNA polymerase activity under these conditions is paralleled by a decrease in the synthesis of viral DNA. But in contrast to the DNA- mutant ts6, where DNA synthesis turns off completely in response to a temperature shift-up, 4-8 continues to synthesize viral DNA for several hours after shift-up at a 10-to 20-fold reduced rate. The results demonstrate that viral DNA is synthesized in the absence of active DNase, yet less efficiently so than in its presence. The possibility that the DNase is responsible for the generation of rapidly sedimenting, concatemeric viral DNA can be excluded since the same proportion of pulse-labeled DNA appears in this fraction for 4-8 as for wild type independent of the temperature. (Author abstract) (19 Refs)

33. MOLECULAR GENETICS OF HERPES SIMPLEX VIRUS. V. CHARACTERIZATION OF A MUTANT DEFECTIVE IN ABILITY TO FORM PLAQUES AT LOW TEMPERATURES AND IN A VIRAL FUNCTION WHICH PREVENTS ACCUMULATION OF CORELESS CAPSIDS AT NUCLEAR PORES LATE IN INFECTION.

Tognon M, Furlong D, Conley AJ, Roizman B
Inst. Microbiology, Univ. Ferrara, Ferrara, Italy
J Virol; 40(3):870-880 1981

In herpes simplex virus-infected cells, coreless capsids accumulate at the nuclear pores soon after infection, but subsequently disappear, suggesting that, as in adenovirus-infected cells, the release of viral DNA from nucleocapsids takes place at the nuclear pores. A nonlethal mutant, HSV-1(50B), produced by mutagenesis of HSV DNA fragments and selected for delayed production of plaques at 31 C, accumulated coreless capsids at the nuclear pores late in infection in contrast to wild-type viruses. Recombinants selected for ability to produce plaques at 31 C by marker rescue with digests of herpes simplex virus 2 DNA and selected cloned fragments of HSV-1 DNA no longer accumulated empty capsids at nuclear pores late in infection. These results suggest that herpes simplex viruses encode a function which prevents accumulation of coreless capsids at nuclear pores, presumably by preventing uptake, unenvelopment, and DNA release from progeny virus, and indicate that the cold sensitivity of plaque formation and accumulation of coreless capsids might be related or comap in the S component of the genome. (Author abstract) (28 Refs)

34. CHARACTERIZATION OF COLIPHAGE LAMBDA HYBRIDS CARRYING DNA FRAGMENTS FROM HERPES SIMPLEX VIRUS TYPE 1 DEFECTIVE INTERFERING PARTICLES.

Denniston KJ, Madden MJ, Enquist LW, Vande Woude G
Div. Molecular Virology, Georgetown Univ. Medical Sch., Rockville, MD, 20852
Gene; 15(4):365-378 1981

Characterization of 34 hybrid lambda bacteriophages carrying Eco RI fragments obtained from DNA of defective interfering particles of the Patton strain of Herpes simplex virus type 1 (HSV-1) is described. Recombinant DNA technology was used to study the structure of individual molecules within the population. Three structural groups of Patton defective DNA (dDNA) Eco RI fragments were defined. All cloned fragments contained S region terminal repeat sequences (TRS) fused to unique HSV-1 DNA. Several fragments contained deletions and rearrangements not described previously for DNA of HSV-1 defective interfering particles. A model describing the generation of defective interfering DNA based on recombination events involving the terminal 'a' sequence is presented. (32 Refs)

35. TRANSFORMATION-DEFECTIVE MUTANT OF ADENOVIRUS TYPE 5 CONTAINING A SINGLE ALTERED E1A MRNA SPECIES.

Carlock LR, Jones NC
Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907
J Virol; 40(3):657-664 1981

A mutant of adenovirus type 5 containing an octanucleotide insert in region E1a of the viral genome was constructed. The insert was present in only one (13s) of the three overlapping mRNA's synthesized from this region. The insert was within the sequences removed by RNA splicing during the production of the other two mRNA's. The insertion resulted in a shift in the translational reading frame of the 13s mRNA and the probable premature termination of translation. The mutant was defective for viral DNA replication in HeLa cells and the transformation of rat embryo and baby rat kidney cells, indicating that a product encoded by the 13s mRNA is required for these two processes. Other early regions of the genome were expressed in HeLa cells infected by this mutant although in some cases the expression was decreased as compared with wild-type-infected cells. (Author abstract) (27 Refs)

36. NUCLEOTIDE SEQUENCE OF THE TRANSFORMING EARLY REGION E1B OF ADENOVIRUS TYPE 12 DNA: STRUCTURE AND GENE ORGANIZATION, AND COMPARISON WITH THOSE OF ADENOVIRUS TYPE 5 DNA.

Kimura T, Sawada Y, Shinawawa M, Shimizu Y, Shiroki K, Shimojo H, Sugisaki H, Takanami M, Uemizu Y, Fujinaga K
Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Nucleic Acids Res; 9(23):6571-6589 1981

The nucleotide sequence of the entire transforming early region Elb of the highly oncogenic adenovirus Type 12 (Ad12) DNA has been determined. The total sequence (3860 base pairs) encompasses the entire transforming early region E1 of AD12 DNA. From the sequence for the Elb region of Ad12, and t he transcription map of the Elb region the structure and gene organization of the early region Elb of Ad12 DNA were analyzed and compared with those of the Elb region in the non-oncogenic Ad5 DNA. Most of the sequences in the Elb region of Ad12 was highly homologous to that of Ad5. It is predicted that the Ad12 region Elb codes for polypeptides of 53.9, 19.1, and 8.9 kd. This situation is identical with that of the Ad5 region Elb which codes for polypeptides of 54.9, 20.6, and 8.3 kd. The function of these predicted polypeptides encoded by the Elb regions in cell transformation is discussed. (Author abstract) (41 Refs)

37. TERMINAL REARRANGEMENTS IN THE GENOME OF ADENOVIRUS TYPE 12 MUTANTS ADAPTED TO GROWTH IN TWO HUMAN TUMOR CELL LINES.

Schwarz E, Reinke C, Yamamoto N, Zur Hausen H
Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Virology; 116(1):284-296 1982

After serial passage of adenovirus type 12 in cells of the human melanoma line Nki-4 virus mutants with enhanced growth potential have been isolated which carry additional sequences of regularly increasing size at the right end of the genome. DNA sequence analysis was performed to characterize these genomic alterations as well as those of the previously described Ad12 C4/1 mutants adapted to growth in the human carcinoma cell line C4/1. Duplication of the inverted terminal repetition (ITR) emerged as the common feature of the right terminal alterations of all the mutant genomes analyzed. The sequences present between the ITR repeats were of either right-end or left-end origin, the latter suggesting that left-end sequences comprising the ITR and parts of the adjacent unique sequences have been transferred to the right end of the genome. The different sizes of the additional sequences in Ad12 Nki-4 DNA could be explained by varying degrees of amplification of a basic additional sequence of 342 base pairs. (Author abstract) (26 Refs)

38. THE REMARKABLE INSTABILITY OF REPLICATION LOOPS PROVIDES A GENERAL METHOD FOR THE ISOLATION OF ORIGINS OF DNA REPLICATION.

Zannis-Hadjopoulos M, Persico M, Martin RG

Lab. Molecular Biology, Natl. Inst. Arthritis, Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 20205

Cell; 27(1,part2):155-163 1981

Closed superhelical replicative intermediates of SV40 DNA were stable during incubation at elevated temperatures for prolonged times. However, when the replicative intermediates were nicked or made linear by digestion either outside or inside of the replication loop, the nascent DNA strands were spontaneously extruded at a measurable rate even at 37 C. The extruded DNA was double-stranded. The rate-limiting step in the extrusion was not the rate of branch migration. The instability of replicati on loops suggested a method for the detection of replication origins. The method has been tested by a reconstruction experiment in which a small amount of linear SV40 replicative intermediates was mixed with a vast excess of cellular DNA. The mixture was heated overnight at 55 C, and the spontaneously extruded nascent strands were isolated and inserted into pBR322. Plasmids containing SV40 DNA of less than genomic size, symmetrically distributed about the SV40 replication origin, were isolated. This result suggests that the method is generally applicable to the isolation of replication origins. (Author abstract) (34 Refs)

39. MUTANT CARRYING DELETIONS IN THE TWO SIMIAN VIRUS 40 EARLY GENES.

Feunteun J, Carmichael G, Nicolas JC, Kress M

Institut de Recherches Scientifiques sur le Cancer, 94802 Villejuif Cedex, France

J Virol; 40(3):625-634 1981

We isolated a simian virus 40 mutant, dl2194, which carried deletions in both early genes. One deletion removed 234 base pairs in the 54/59 region within the small-t-antigen coding sequence and the large-T-antigen gene intron. The second deletion removed 57 base pairs at the C terminus of the large-T-antigen coding sequence (0.20 map unit). dl2194 was a viable mutant; it carried a normal helper function for adenovirus growth on monkey cells, and it displayed the transformation properties of a small-t-antigen-negative single mutant. Therefore, none of the known large-T-antigen functions seemed to be altered by the C-terminal deletion. (Author abstract) (34 Refs)

40. THREE SEGMENTS FROM THE MONKEY GENOME THAT HYBRIDIZE TO SIMIAN VIRUS 40 HAVE COMMON STRUCTURAL ELEMENTS.

Queen C, Lord ST, McCutchan TF, Singer MF
Lab. Biochemistry, NCI, Bethesda, MD, 20205
Mol Cell Biol; 1(12):1061-1068 1981

Recently, three cloned segments were isolated from a monkey genomic library. The segments hybridizing to the HindIII-C fragment of the DNA virus, simian virus 40 (SV40) are discussed. The primary structure of one segment has been reported. As a further step in analyzing the relationship between the SV40-hybridizing segments and SV40 itself, the sequence and genomic arrangements of the other two cloned segments was determined by previously described methods, and a comparison was made of all three. The SV40 hybridizing region in each segment was limited to several hundred base pairs. All segments contained multiple and disconnected sequences homologous to the region of SV40 directly surrounding the viral replication origin. While the number and arrangement of the homologous sequences was different in the three segments, each had the following features in common: (1) each contained multiple copies of the sequence GGGCGGPuPu, which also appeared 6x near the origin of SV40, (2) each contained several strong homologies to the central dyad symmetry of SV40, and (3) each contained a long internal repeat, as did the origin region of SV40. These three SV40 hybridizing segments are members of a larger family of genomic sequences that hybridize well to each, but not necessarily to SV40. (18 Refs)

41. LATE MESSENGER RNA PRODUCTION BY VIABLE SIMIAN VIRUS 40 MUTANTS WITH DELETIONS IN THE LEADER REGION.

Piatak M, Subramanian KN, Roy P, Weissman SM
Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Mol Biol; 153(3):589-618 1981

We have analyzed the structure of simian virus 40 messenger RNA in cells infected with mutant viruses in which DNA encoding various segments of the late leader has been deleted. The results show that large amounts of stable unspliced mRNA may accumulate in the cytoplasm and that some unspliced RNA appears in polyribosomes. The locations of the prominent 5' ends of mRNA are influenced by relatively remote downstream sequences and bear no fixed relationship to any sequence of the simian virus 40 DNA retained in the mutant virus. Sequences downstream from the leader template may play a role in determining the region in which transcription initiates preferentially. Splices may occur even when nucleotides further than seven residues downstream from the upstream end of the splice are altered, and alternative splices with one junction in common may be differently affected by deletions near the common splice junction. (Author abstract) (64 Refs)

42. MOLECULAR CLONING OF VIRAL DNA FROM HUMAN GENITAL WARTS.

de Villiers EM, Gissmann L, Zur Hausen H
Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, 7800 Freiburg, W. Germany
J Virol; 40(3):932-935 1981

The DNA of human papilloma virus Type 6 (HPV 6) has been cloned in Escherichia coli K-12 by using pBR322 as vector. The DNA was cloned at the BamHI and EcoRI cleavage sites. This DNA was mapped by employing further restriction endonucleases and by terminal labeling. No major differences were noted as compared to HPV 6 DNA originating directly from a genital wart. The existence of at lest two DNA subtypes (HPV 6a and 6b) became apparent. (Author abstract) (18 Refs)

43. SEQUENCES AT THE CAPPED 5'-ENDS OF POLYOMA VIRUS LATE REGION MRNAS: AN EXAMPLE OF EXTREME TERMINAL HETEROGENEITY.

Cowie A, Tyndall C, Kamen R
Transcription Lab., Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
Nucleic Acids Res; 9(23):6305-6322 1981

We have localized with respect to the genomic DNA sequence the capped 5'-termini of polyoma virus late region mRNAs. A minimum of fifteen different purine termini were found within a 94 base pair region (66.36 to 68.12 map units, nt 5075-5168) immediately preceding the sequence determining the late region mRNA leader repeat (1-3). The most common termini occur at nearly every possible purine within a 25 bp sequence proximal to the leader repeat unit. These do not bear the usual positional relationship to a sequence resembling the 'TATA' box consensus. Deletion mutants lacking minor cap sites and sequences upstream from the principal cap sites were viable. A deletion mutant lacking one of the principal cap sites formed small plaques, while a slightly larger deletion further impinging on the principal cap site region was non-viable. The principal cap sites, which we assume to be transcriptional initiation points, are included in a DNaseI hypersensitive region of polyoma virus chromatin. (Author abstract) (51 Refs)

44. STRUCTURE OF THE BABOON ENDOGENOUS VIRUS GENOME: NUCLEOTIDE SEQUENCES OF THE LONG TERMINAL REPEAT.

Tamura T, Noda M, Takano T
Dept. Microbiology, Keio Univ. Sch. Medicine, Shinjuku-ku, Tokyo, Japan
Nucleic Acids Res; 9(23):6615-6626 1981

The entire nucleotide sequence of the long terminal repeat (LTR) of baboon endogenous virus (BaEV) M7 was determined, which consisted of 554 base pairs (bp). At both ends of the LTR, 13 bp sequences, AAATGAAAAGTAA and TGATTCTAACATC, were detected to be inverted repeats. The structure with these inverted repeats resembles those of other retroviruses and transposable elements. A Hogness box, TATAAAA, and a putative poly(A)-addition signal, AGTAAA, were present within the right-hand half of the LTR, where the initiation and termination of the viral RNA synthesis seems to occur in the integrated BaEV genome. The primer-binding site of at least 14 bp long was found just outside of the LTR where the strong stop DNA started, and the primer for reverse transcription in BaEV seemed to be tRNA-Pro. Several structural features are commonly detected in the LTRs of BaEV and other retroviruses. Our studies suggest that BaEV has evolved from a common ancestor with other mammalian Type C viruses. Close relationships between BaEV and a feline endogenous virus, RD114, are demonstrated. (Author abstract) (33 Refs)

IMMUNOLOGICAL STUDIES

45. PRODUCTION AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES AGAINST THE EPSTEIN-BARR VIRUS MEMBRANE ANTIGEN.

Strnad BC, Schuster T, Klein R, Hopkins RF, Witmer T, Neubauer RH, Rabin H
Frederick Cancer Res. Center, Frederick, MD, 21701
J Virol; 41(1):258-264 1982

Five murine hybridoma lines that produce monoclonal antibodies against Epstein-Barr virus membrane antigen (MA) were established. Immunoprecipitation experiments demonstrated that three of the antibodies precipitated both the 236,000 (236K) MA and the 212K MA. The other two antibodies precipitated the 86K MA. Antibodies against the 236K-212K MA and the 86K MA mediated complement-dependent cytolysis of Epstein-Barr-virus-infected cells. The antibodies against the 86K MA neutralized both the B95-8 and P3HR-1 viruses. (Author abstract) (18 Refs)

46. DETECTION OF EPSTEIN-BARR VIRAL DNA INTERNAL REPEATS IN THE NASOPHARYNGEAL MUCOSA OF CHINESE WITH IGA/EBV-SPECIFIC ANTIBODIES.

Desgranges C, Bornkamm GW, Zeng Y, Wang PC, Zhu JS, Shang M, De-The G
CNRS Lab., Faculty Medicine Alexis Carrel, 69372 Lyon Cedex 2,, France
Int J Cancer; 29(1):87-91 1982

Fifty-six South Chinese individuals exhibiting IgA antibodies to EBV for 18 mo and presenting nasopharyngeal abnormalities were biopsied. Four nasopharyngeal carcinomas, two at a very early stage, were detected. In 14 other individuals, without clinical or histopathological evidence of tumor, EBV/DNA internal repeats and/or EBNA were detected in the biopsied mucosae. The presence of IgA/EBV antibodies and/or EBV markers in the nasopharyngeal mucosa may characterize pre-cancerous conditions. (Author abstract) (25 Refs)

47. NASOPHARYNGEAL CARCINOMA AND EPSTEIN-BARR VIRUS (EBV)-SPECIFIC IGA.

Desgranges C
Laboratorie d'Epidemiologie et Immunovirologie des Tumeurs CNRS, Faculte de Medecine Alexis Carrel, rue Guillaume-Paradin, 69372 Lyon Cedex 2, France
Pathol Biol (Paris); 29(10):587-589 1981

Studies on EBV-specific IgA in patients with nasopharyngeal carcinoma are reviewed. EBV-specific IgA was found in sera of some subjects in whom nasopharyngeal carcinoma was diagnosed several yr later. Anti-virus capside IgA from the lymphoepithelial mucosa of the nasopharynx can be considered a means of early detection of nasopharyngeal cancer. (18 Refs) (In FRE)

48. CHLAMYDIA TRACHOMATIS AND HERPES SIMPLEX VIRUS IGA ANTIBODIES IN CERVICAL SECRETIONS OF PATIENTS WITH CERVICAL ATYPIA.

Kalimo K, Terho P, Honkonen E, Gronroos M, Halonen P
Dept. Dermatology and Venereology, Univ. Turku, 20520 Turku 52, Finland
Br J Obstet Gynaecol; 88(11):1130-1134 1981

The association of Chlamydia trachomatis (CT) and herpes simplex virus (HSV) with malignant or premalignant changes in the cervix uteri was studied by determining immunoglobulin A (IgA) antibodies in the cervical secretions of 28 women with inflammatory, 28 with dysplastic 7 with malignant changes of the uterine cervix, and 26 healthy controls. In cervical secretions IgA antibodies to CT were found in 24 of 35 (69%) patients with malignant or premalignant changes, in 11 of 28 (39%) with cervicitis and in 3 of 26 (12%) controls. IgA antibodies to HSV were found in 10 of 35 (28%) patients with malignant atypia or dysplasia but in none of the women with cervicitis or the controls. The highest frequency of antibodies was found in the patients with cervical carcinoma. Serum IgA antibodies to CT and HSV were found equally in the patients and the controls. Our results suggest that in patients with cervical atypia, local IgA CT antibody production occurs. Whether this association is etiological or coincidental cannot be concluded from this study. (Author abstract) (13 Refs)

49. NEW ANTIGEN INDUCED BY HERPES SIMPLEX VIRUS IN HUMAN TUMORS.

Posevaia TA, Kosiakova NP, Barinskii IF, Kosiakov PN, Pavliuchenkova RP
D. I. Ivanovskii Inst Virology, Moscow, USSR
Vopr Virusol; (5):597-601 1981

Infection of biopsy specimens of various human tumors with herpes simplex virus was found to induce a new antigen not only in neoplasms of the uterus, cervix, and ovary but also in those of the kidney and bladder. The antigens induced in the cervical carcinoma had the highest complement-fixation activity. (13 Refs) (In RUS)

50. IMMUNOLOGIC CROSS-REACTION BETWEEN LARGE T-ANTIGENS OF SV40 AND POLYOMA VIRUS.

McCormick F, Lane DP, Dilworth SM
(c/o Dilworth), Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Virology; 116(1):382-387 1982

Serum containing a high titer of antibodies against SV40 T-antigen was produced in rabbits, using D2 protein as immunogen. This protein was purified from cells infected with adenovirus-SV40 hybrid virus Ad2+D2. Anti-D2 serum recognized SV40 large T, but not small T. In addition, it was able to immunoprecipitate polyoma virus large T, demonstrating that these proteins share antigenic determinants. The titer of this antiserum against polyoma virus large T was comparable to the titers of polyoma virus antitumor sera. Anti-D2 serum did not immunoprecipitate polyoma virus middle T or small T antigens. The activity against polyoma virus large T was sensitive to SDS denaturation. (Author abstract) (24 Refs)

51. A CONTROLLED STUDY OF HEPATITIS CORE ANTIBODY (HBCAB) IN PRIMARY HEPATOCELLULAR CARCINOMA AND LIVER CIRRHOSIS IN KENYA.

Bowry TR, Shah MV, Ahmad Z
Immunology Section, Dept. Human Pathology, Univ. Nairobi, Nairobi, Kenya
East Afr Med J; 58(8):576-582 1981

Incidence of hepatitis B virus (HBV) markers was studied in 75 Kenyan patients with confirmed liver disease. Among these patients, 15 had liver cirrhosis (LC), 13 had LC and concomitant primary hepatocellular carcinoma (PHC), and 47 had PHC. Presence of hepatitis B surface antigen (HBsAg) was detected in 40% of the patients with LC, in 47% of the patients with LC + PHC, and in 46% of the patients with PHC.

Among the HBsAg-positive patients, high titers of hepatitis B core antibody (HBcAb) were detected in 100% of the patients with LC, 100% of those with LC + PHC, and 90% of those with PHC. HBcAb as a sole marker of HBV was detected in 13% of the patients with LC, 31% of those with LC + PHC, and 9% of those with PHC. (16 Refs)

52. SEROLOGIC PROFILE AND POSSIBLE ETIOLOGIC FACTORS IN PRIMITIVE CARCINOMA OF THE LIVER.

Caporaso N, Giardullo N, Servillo F, Del Vecchio-Blanco C, Coltorti M

Istituto di Semeiotica Medica, I Facolta di Medicina e Chirurgia, Universita di Napoli, Napoli, Italy

Fegato; 27(1):55-57 1981

The relationship between primitive carcinoma of the liver (PCL) and chronic infection with virus B (CIVB) was studied using radioimmunoassay. CIVB seems to play an important role in the etiology of PCL, especially in areas of high incidence of CIVB. Of 612 patients with evolutive liver pathology, 32 (36-83 yr old, 27 men and 5 women) had PCL. In 23 patients PCL was associated with cirrhosis (ALC); of these 9 had acute progressive hepatitis, 6 were alcoholics, and 7 had blood relatives who had died from PCL. Diagnosis was confirmed by biopsy (obtained through laparoscopy), scintigraphy, alpha1-fetoprotein, and routine blood chemistry. Nine patients had negative results for all serological markers, 11 had positive results for HBsAg+, 4 for anti-HBc+, and 8 for both anti-HBc+ and anti-HBs+. Of the 11 HBsAg+ positive cases, only 2 were associated with 'e' positive results, indicating that the infection with virus B had occurred long ago. No patients reported exposure to toxic industrial products, or contaminated food, or prolongued use of sexual hormones or their derivatives. PCL was frequently associated with CIVB even in non-ALC cases. (5 Refs) (In ITA)

53. DIAGNOSIS OF PRIMARY BREAST CARCINOMA THROUGH IMMUNOHISTOCHEMICAL DETECTION OF ANTIGEN RELATED TO MOUSE MAMMARY TUMOR VIRUS IN METASTATIC LESIONS: A REPORT OF TWO CASES.

Mesa-Tejada R, Oster MW, Fenoglio CM, Magidson J, Spiegelman S

Inst. Cancer Res., 701 West 168th St., New York, NY, 10032

Cancer; 49(2):261-268 1982

Recent investigations have established that approximately half of human breast carcinomas contain an immunohistochemically detectable antigen which is cross-reactive with the 52,000-dalton major glycoprotein (gp52) of the mouse mammary tumor virus (MMTV). This antigen can be localized in paraffin-embedded sections of routinely fixed tissues using heterologous antibodies to gp52 or MMTV. This report describes two patients with metastatic carcinoma in axillary lymph nodes without any clinical evidence of a primary lesion in the breast or elsewhere. The localization of the gp52-related antigen in paraffin-embedded sections of both metastatic lesions suggested the presence of primary mammary carcinoma. In both instances, this suggestion was ultimately confirmed by the finding of primary lesions in which the gp52-related antigen was also found. (Author abstract) (30 Refs)

VIRAL STUDIES IN HUMAN CANCER

54. BURKITT'S LYMPHOMA.

Ambrus JL, Ambrus CM

Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

J Med; 12(6):385-413 1981

Clinical and epidemiologic features of Burkitt's lymphoma are reviewed. Epidemiologic studies suggest that simultaneous infection with Epstein-Barr (E-B) virus and malaria may be involved as etiologic agents. On the other hand we have found that in the Amazon region of Brazil and Peru both malaria and E-B virus infection is common among children, yet Burkitt's lymphoma is rare. The possibility exists that other concomitant etiologic agents and genetic factors are also involved. Several investigators suggested the possible involvement of Reo 3 virus. We have found antibodies against Yaba virus. A laboratory worker who accidentally inoculated himself with Yaba virus developed a histiocytoma which when inoculated into Asiatic monkeys produced typical Yaba tumors. This was the first case that Koch's postulates were fulfilled in a virus induced neoplasm in man. Therapeutically, the best clinical results were obtained in those patients who were treated with small doses of cyclophosphamide. On the basis of somewhat inadequate follow-up studies, it is estimated that '5 year cures' were obtained in about 10% of the patients. (Author abstract) (44 Refs)

55. PRESENCE OF EPSTEIN-BARR VIRUS DNA IN TONSILLAR TISSUES.

Brichacek B, Suchankova A, Hirsch I, Sibl O, Rezacova D, Zavadova H, Vonka V

Dept. Experimental Virology, Inst. Sera and Vaccines, 101 03 Prague, Czechoslovakia

Acta Virol (Praha); 25(6):361-370 1981

Sera from 48 tonsillar carcinoma (TC) patients, 48 matched controls and 16 recurrent exudative tonsillitis (RET) patients were examined for the presence of Epstein-Barr virus (EBV) associated nuclear antigen (EBNA), early antigen (EA) and virus capsid antigen (VCA). Higher prevalence and significantly higher antibody titers against all three EBV-associated antigens were observed in TC patients in comparison with controls and RET patients. Patients suffering from anaplastic TC had higher titers of antibodies against VCA and EA than TC patients with other histological diagnoses. Five out of 11 TC biopsies obtained from nine patients were positive for EBV DNA at levels of 0.17, 4 to 5, 15 to 18 and in two cases 3 EBV genome equivalents per cellular genome. Among 16 RET patients, 4 were found positive at levels not exceeding 2.17 EBV genome equivalents per cellular genome. Higher titers of antibody against all EBV antigens were found in TC and RET patients with EBV DNA-positive tonsillar tissue than in those with EBV DNA negative tonsillar tissue. (Author abstract) (34 Refs)

56. GASTRITIS, PEPTIC ULCER DISEASE, INFLAMMATORY BOWEL DISEASE, AND STOMACH AND COLON CANCERS - ARE THEY ALL CAUSED BY VIRAL INFECTIONS?

Waldum HL, Bjorvatn B, Burhol PG

Dept. Medicine, Univ. Hosp. Tromso, Tromso 9012, Norway

Med Hypotheses; 7(11):1329-1338 1981

A hypothesis considering that chronic gastritis and ulcerative colitis are induced by viral infections, and that such chronic infection of the mucosa may lead to ulceration and occasionally cancer, is proposed. Since gastric ulcers occur almost exclusively together with gastritis, it is conceivable that both disease may reflect an infection with the same virus, perhaps cytomegalovirus; also is considered that the increased vagal tone in patients with duodenal ulcers may be caused by viral involvement of the vagal ganglion. In patients with dyspepsia without gastritis or peptic ulcer, the virus may remain in the vagus ganglion, affecting afferent nerves leading to pain and discomfort. Gastric cancer occurs almost exclusively in patients with gastritis, and patients with gastric ulcer disease have an increased risk of developing gastric cancer. In addition, patients with immune defects have an increased frequency of gastritis and gastric cancer. A common etiology of gastritis, gastric ulcer, and gastric cancer is suggested. Duodenal ulcers and Crohn's disease may be due to activation of latent viral infection of the corresponding neural ganglions, with subsequent migration of virus along the nerves to the gut wall. Ulcerative colitis may be caused by cytomegalovirus. If ulcerative colitis has a viral etiology, it is reasonable to assume that the same virus may predispose to malignant cell transformation in the colon mucosa. Colon polyps may also be caused by chronic viral infections. The similarities between gastritis, gastric ulcer disease, gastric cancer, duodenal ulcer disease and non-ulcer dyspepsia on one hand and ulcerative colitis, colon cancer, Crohn's disease and irritable colon on the other, are discussed. (46 Refs)

57. HUMAN PAPILLOMAVIRUS (HPV) IN CONDYLOMATOUS LESIONS OF CERVIX: A COMPARATIVE ULTRASTRUCTURAL AND IMMUNOHISTOCHEMICAL STUDY.

Ferenczy A, Braun L, Shah KV
Dept. Pathology, Jewish General Hosp., 3755 Chemin de la Cote Ste. Catherine, Montreal, Quebec H3T 1E2, Canada
Am J Surg Pathol; 5(7):661-670 1981

Cervical condylomata classified histologically as flat, papillary, or endophytic were obtained from 97 patients (16-35 yr old). Transmission electron microscopy (TEM) was used to detect the presence of human papillomavirus (HPV) particles; the immunoperoxidase technique (IPT) was used to detect viral antigen. HPV particles were found in 24/97 specimens by TEM. Viral particles were demonstrated in 21/68 flat and 3/26 papillary condylomata. Viral antigen was found in 47/97 specimens by IPT. All specimens positive by TEM were also positive by IPT, confirming the specificity of the immunological staining. The viral antigen was detected in 38/68 specimens of flat condylomata, in 9/26 papillary condylomata, and in 0/3 endophytic condylomata. Prevalence of HPV correlated with the extent of koilocytosis rather than with histiotype. IPT is of value for further characterizing cervical condylomata and the relationship between HPV infection and cervical intraepithelial neoplasia. (23 Refs)

58. PRIMARY HEPATOCELLULAR CARCINOMA – ETIOLOGY, PATHOGENESIS, AND PREVENTION.

London WT
Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Hum Pathol; 12(12):1085-1097 1981

Worldwide, primary hepatocellular carcinoma may be the most common cancer in men. Usually it occurs in association with cirrhosis or chronic hepatitis. In this article I present evidence that the majority of these cases are associated with, and probably caused by, persistent infection with hepatitis B virus. I also propose a model that describes the role of the hepatitis B virus in the pathogenesis of primary hepatocellular carcinoma. If persistent infection with hepatitis B virus is required for the development of most cases of primary hepatocellular carcinoma, prevention of such infections should prevent most cases of primary hepatocellular carcinoma. A vaccine against hepatitis B virus, prepared from surface antigen particles (HBsAg) harvested from the blood of hepatitis B virus carriers, has been safe and effective in preventing acute infection with hepatitis B virus in adult homosexual men. If it is equally safe and effective in young children, it will be administered widely to populations living in areas endemic for hepatitis B virus infections. Thereafter it may be possible to learn within 5 to 10 years whether the vaccine prevents chronic liver disease. If it does, it will be reasonable to conclude that it will also prevent primary hepatocellular carcinoma. (Author abstract) (47 Refs)

59. WHO WORLD CAMPAIGN AGAINST CANCER: ONE CASE OF CANCER IN THREE CAN BE PREVENTED. PRIORITY OF FIGHT AGAINST FOUR TUMOR TYPES.

Stjernsward J
WHO Cancer Unit, Geneva, Switzerland
Lakartidningen; 78(46):4128-4130 1981

Based on the knowledge of cancer-causing agents and circumstances, the Committee on Cancer of World Health Organization has given priority to the battle against four types of cancer, which can be prevented by eliminating their causes. They include cancer of the mouth, lungs, liver, and uterine cervix. Chewing of tobacco and betel is a major cause of cancer of the mouth. Cigarette smoking is the principal cause of lung cancer in developed countries, but the incidence of smoking is increasing in third world countries, which may lead to a corresponding increase in lung cancer incidence there. Hepatitis B virus is a major cause of primary liver cancer along with aflatoxins. Reduction of the incidence of cancer of the uterine cervix is expected from better genital hygiene. (no Refs) (In SWE)

60. THE HEPATITIS-B VIRUS AND HEPATOCELLULAR CARCINOMA.

Kew MC
Dept. Medicine, Witwatersrand Univ. Medical Sch., Johannesburg, South Africa
Semin Liver Dis; 1(1):59-67 1981

The association between hepatocellular carcinoma (HCC) and chronic hepatitis-B virus (HBV) is discussed, and various explanations for its etiology are considered. The world-wide geographic distributions of the HBV carrier state and HCC are remarkably similar, with some exceptions. Countries in sub-Saharan Africa and the Far East, eg, with HBV surface antigen carrier rates of 6-14% also have the highest rates of HCC. However, in Greenland, where 7-25% of the population has chronic HBV surface antigen, HCC is nevertheless rare. This discrepancy could be explained by the absence of a cocarcinogen in the Greenland environment. The most persuasive evidence that an association exists between HCC and HBV is the frequency with which markers of the virus are present in the serum and tissues of patients with this tumor. Alternative explanations to a cause and effect relationship between HBV infection and HCC are discussed. However, no such considered explanations account for the association as well as the postulate that HBV plays a causal role in HCC. (84 Refs)

61. DETECTION OF THE HUMAN T CELL LYMPHOMA VIRUS P19 IN CELLS OF SOME PATIENTS WITH CUTANEOUS T CELL LYMPHOMA AND LEUKEMIA USING A MONOCLONAL ANTIBODY.

Robert-Guroff M, Ruscetti FW, Posner LE, Poiesz BJ, Gallo RC
Lab. Tvmor Cell Biology, NCI, NIH, Bethesda, MD, 20205
J Exp Med; 154(6):1957-1964 1981

The p19 monoclonal antibody for human T cell lymphoma virus (HTLV) and expression of HTLV p19 in cells of patients with leukemia and lymphoma are described. Radioimmune precipitation assay for HTLV proteins demonstrated the specificity of the antibody. Among the iodinated HTLV proteins, only p19 could be specifically precipitated. In indirect immune fluorescence assays, anti-p19 specifically labeled only HTLV-producing cells. Transformed HUT78 cells, derived from a patient with either cutaneous T cell lymphoma or leukemia (CTLC), did not produce HTLV and were negative for p19. Both HUT102 parental cells and clones were 60-70% positive, suggesting that viral expression might be related to cell cycling. CTCL-2 and CTCL-3 cells were 5% and 12% positive, respectively. The fluorescent labeling of virus-positive cells was restricted to the cell membrane. Only fixed cells were labeled, supporting the idea that p19 is an internal HTLV protein and not an envelope component. HTLV p19 is not expressed in most malignant T cells, indicating that replicating HTLV is not present. The monoclonal antibody to HTLV p19 provides an assay of HTLV expression for determining the frequency of HTLV replication in human T cells and for studying the regulation of viral gene expression. (14 Refs)

62. SYNTHESIS OF A VIRAL PROTEIN WITH MOLECULAR WEIGHT OF 30,000 (P30) BY LEUKEMIC CELLS AND ANTIBODIES CROSS-REACTING WITH SIMIAN SARCOMA VIRUS P30 IN SERUM OF A CHRONIC MYELOID LEUKEMIA PATIENT.

Derks JP, Hofmans L, Bruning HW, Rood JJ
Dept. Immunohematology, Bloodbank, Univ. Hosp., Building 23, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands
Cancer Res; 42(2):681-686 1982

We studied a patient with a Philadelphia chromosome-positive chronic myeloid leukemia, who died in relapse after multiple transfusions and grafting with bone marrow from his monozygotic twin brother (referred to as 'donor' in this paper). We present data indicating that this patient may have had a retrovirus infection and that this virus is related to the group of exogenous primate Type C retroviruses. Antibodies to simian sarcoma virus (SSV) mol wt 30,000 protein (p30) but not endogenous feline virus RD-114 could be found in patient but not donor serum. Patient but not donor cells were able to actively synthesize a p30 protein that could be precipitated with patient serum and rabbit anti-SSV p30 but not with donor serum or rabbit anti-RD-114 p30. Patient p30 resembles SSV p30 but not RD-114 p30 in peptide mapping by limited proteolysis and subsequent slab gel electrophoresis. Patient but not donor cells were able to actively synthesize a mol wt 78,000 protein that could be precipitated with goat anti-SSV An enzyme with properties of reverse transcriptase was increased 30-fold in patient cells when compared with donor and other control cells. Related to the presence of widespread infectious agents may be the finding that, in the course of the patient's disease, donor serum showed increasing amounts of possibly immunoregulatory antibodies, reactive with autologous and, more effectively, with patient-derived cell membrane mol wt 80,000 protein (a possible idiotypic receptor structure) and mol wt 94,000 protein (a T-cell alloantigen). (Author abstract) (31 Refs)

63. DETECTION BY RADIOIMMUNOASSAY OF ANTIGENS RELATED TO THE P30 POLYPEPTIDES OF PRIMATE TYPE C ONCOVIRUSES IN PERIPHERAL LEUKOCYTES FROM PATIENTS WITH CHRONIC MYELOGENOUS LEUKAEMIA.

Toth FD, Vaczi L, Kiss J, Rethy A, Kiss A, Rak K
Inst. Microbiology, Univ. Medical Sch., 4012 Debrecen, Hungary
Acta Virol (Praha); 25(6):376-380 1981

Leukocytes from patients with chronic myelogenous leukemia were examined for antigens related to the p30 polypeptides of baboon endogenous virus (BaEV) and gibbon ape leukemia virus (GaLV). Samples from patients with the quiescent phase of the disease proved to be negative or contained p30 of BaEV as the only viral antigen. In cases of blastoid crisis or acceleration, an antigen related to p30 of GaLV could be detected. In five of six patients, acceleration or blastoid crisis was preceded by expression of GaLV p30. (Author abstract) (15 Refs)

64. BIOCHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF CELLULAR DNA POLYMERASES ALPHA, BETA AND GAMMA, AND A REVERSE TRANSCRIPTASE FROM HUMAN MELANOMA TISSUE.

Chandra P, Balikcioglu S, Mildner B
Zentrum der Biclogischen Chemie, Theodor-Stern-Kai 7, D-6 Frankfurt a. Main 70, W. Germany
Cell Mol Biol; 27(2/3):239-251 1981

The present study describes separation and purification of a reverse transcriptase and cellular DNA polymerases from human primary melanoma tissue. The specific requirements with respect to bivalent cations and template-primers for DNA polymerase alpha, DNA polymerase beta and DNA polymerase gamma, as well as for the reverse transcriptase, are reported. Sodium dodecylsulfate gel electrophoresis of the purified enzymes gave estimated values of mol wt of 160,000, 38,000, 100,000 and 68,000 daltons for DNA polymerase alpha, DNA polymerase beta, DNA polymerase gamma and reverse transcriptase respectively. Serological studies have shown that the reverse transcriptase of human melanoma tissue is not antigenically related to cellular DNA polymerase alpha, beta, or gamma, but is antigenically related to reverse transcriptases from baboon endogenous virus (BEV) and RD-114. This is the first human reverse transcriptase showing cross-reactivity to DNA polymerases from endogenous retroviruses. (Author abstract) (24 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

65. CELLULAR MUTATIONS AND DRUG RESISTANCE PROBED BY HERPES SIMPLEX VIRUS.

Campisi J, Pardee AB
Sidney Farber Cancer Inst., Boston, MA, 02115
J Cell Physiol; 109(3):469-480 1981

Inhibition of herpes simplex virus (type-1) (HSV-1) plaque formation in African green monkey kidney (Vero) cell lines occurred in varying degrees when cultures were exposed to the following drugs: thioguanine (TG), cytosine arabinoside (AraC), methotrexate (MTX), 5-fluorodeoxyuridine (5-FUdR), 5-fluorouracil (5-FU), and bleomycin (BLM). Viral immunofluorescence was substantially reduced when HSV-1-infected human foreskin fibroblasts strain FS2 were exposed to the six drugs, except in the case of BLM, which was cytotoxic and had no antiviral effect. Fluorescence studies showed that TG markedly decreased viral growth in normal FS2 cells while such growth was unaffected in Lesch-Nyhan strain fibroblasts, a strain genetically resistant to killing by TG. While thymidine kinase-deficient HSV-1 (TK[-]HSV-1) did not grow in the normal mouse fibroblast line A31 in the presence of 5-FUdR, a TK-deficient derivative of A31 permitted such growth at low to moderate doses of 5-FUdR. HSV-1-infected xeroderma pigmentosum (group A) (XPA) fibroblasts and FS2 cells were UV-irradiated with 100 microwatts/square cm; immunofluorescence showed that viral activity declined much faster with increasing UV dose in XPA than in FS2 cells. In another experiment TG was effective in reducing HSV-1 fluorescence in one strain of human neck squamous carcinoma cells (SCC-15), but was relatively ineffective in another strain (SCC-25). (21 Refs)

66. DNA AND HISTONE SYNTHESIS IN BUTYRATE-INHIBITED BSC-1 CELLS INFECTED WITH SV40.

Daniell E, Burg JL, Fedor MJ
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Virology; 116(1):196-206 1982

The effect of butyrate on DNA synthesis, histone synthesis, and virus production in SV40-infected monkey cells has been studied. When cells in which DNA and histone synthesis have been blocked by treatment with butyrate are infected with SV40, DNA synthesis is induced to a level at least equal to that in untreated infected cells. Both viral and cellular DNA sequences are replicated. Viral DNA synthesized is predominantly SV40 Form I. The amount of viral DNA which accumulates is reduced by 10-fold in the presence of butyrate, and the yield of infectious virus is lowered 100-fold. Histone synthesis in these cells is stimulated concomitantly with DNA synthesis. The hyperacetylation of histones characteristic of butyrate-treated cells is unchanged by SV40 infection; the newly synthesized histones are hyperacetylated. Thus the mechanism by which butyrate blocks DNA and histone synthesis is not directly related to the hyperacetylation of histones. (Author abstract) (30 Refs)

67. PRODUCTION AND CHARACTERIZATION OF MARMOSET LYMPHOBLASTOID INTERFERON.

Abb J, Abb H, Deinhardt F
Max von Pettenkofer-Institut, Pettenkoferstrasse 9a, D-8000 Munchen 2, W. Germany
Int J Cancer; 29(1):77-80 1982

We describe the production of marmoset lymphoblastoid cell interferon (IFN). Optimal yields of IFN were obtained when EBV-transformed lymphoblastoid cell lines (LCL) at a cell density of 1 x 10(6)/ml were incubated with 100 HAU Sendai virus/ml for 24 hr. Sendai-virus-induced marmoset lymphoblastoid cell IFN was acid-stable and exerted antiviral activity on both homologous and heterologous human cells, thus allowing its classification as IFN alpha. Marmoset lymphoblastoid cell IFN did not inhibit the growth of herpesvirus-transformed marmoset T- or B-cell lines, but markedly enhanced marmoset NK-cell activity against human myeloid leukemia target cells. The use of lymphoblastoid cell IFN in marmosets in vivo may contribute to an understanding of the pathogenic role of IFN in herpesvirus-induced lymphoproliferative diseases. (Author abstract) (15 Refs)

68. LACK OF INTERFERON-INDUCED TRANSFER OF VIRAL RESISTANCE AGAINST MURINE LEUKEMIA VIRUS OR POLIOVIRUS IN COCULTIVATED CELLS.

Mozes LW
Papanicolaou Cancer Res. Inst., Miami, FL, 33101
Virology; 116(1):359-362 1982

It has recently been reported that there can be a transfer of the interferon (IFN)-induced viral resistance between cocultivated animal cells. However, in those systems the challenge virus was capable of replicating in both cell types. A more convincing conclusion could be obtained if the infecting virus could not replicate in the cell type which is homologous to the species of IFN that is added to the cultures. An inhibition of the yield of this virus would indicate that there was a transfer of the antivira l state from one cell species to another. In cocultivated mouse and human cells, a murine ecotropic Type-C virus can only multiply in the mouse cells whereas poliovirus will only replicate efficiently in the human cells. It is clearly evident from this study that only homologous but not heterologous fibroblast IFN is capable of inhibiting the replication of either of these viruses in various combinations of cocultivated cells. (Author abstract) (13 Refs)

GENERAL REVIEWS

69. CYTOMEGALOVIRUS AND THE OTOLARYNGOLOGIST.

Strauss M
Div. Otolaryngology, Milton S. Hershey Medical Center, Hershey, PA, 17033
Laryngoscope; 91(12):1995-2006 1981

Human cytomegalovirus (CMV) is ubiquitous and has been documented as the etiologic factor in several diseases ranging from respiratory tract infection to congenital deafness. Special clinical manifestations of CMV of interest to the otolaryngologist are presented as related to the temporal bone and audiovestibular system, the facial nerve, the aerodigestive tract, the thyroid, and the hematopoietic-lymphoreticular system, and salivary gland. In addition current concepts of CMV oncogenic potential are discussed as they relate to head and neck neoplasms. The results of a study performed on surgical pathology specimens obtained from 26 patients, in an attempt to isolate CMV in tissue culture from salivary gland and/or neoplasms of the head and neck, detected no evidence of viral presence. The significance of these findings and the role of future research is discussed. (Author abstract) (77 Refs)

70. THE DISSECTION AND RECONSTRUCTION OF GENES AND CHROMOSOMES (NOBEL ADDRESS).

Berg P
Dept. Biochemistry, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Angew Chem; 93(10):885-893 1981

The development of understanding of the structure and function of genes and chromosomes is reviewed. Early research established that genes controlled the production of proteins. Analysis of DNA from viruses and bacteria disclosed the double-helix structure and purine-pyrimidine base-pair composition of DNA. Studies with polyoma and SV40 viruses allowed mapping of genes producing specific proteins. SV40 was shown to have different life cycles in primate and non-primate cells. Transformation of host cells by SV40 viruses was demonstrated, indicating that viruses could produce heritable changes in host-cell genetic material. Recombination experiments combined viral DNA from SV40 and bacterial DNA from Escherichia coli. Viral and bacterial DNA have since been incorporated into the genome of mammalian cells. Mammalian cells with bacterial genes have been shown to produce bacterial enzymes and to utilize metabolic pathways not used by normal cells. Findings of recombinant genetic studies have potential applications in medicine for correction of genetic defects and other problems. (49 Refs) (In GER)

71. ROLE OF ONCOGENES IN THE DEVELOPMENT OF TUMORS.

Klein G
Institutionen for tumorbiologi, Karolinska institutet, Stockholm, Sweden
Lakartidningen; 78(41):3575-3577 1981

Recent studies in viral oncogenes are reviewed. The coupling of some normal genes is a common feature of all tumor transformation processes caused by not directly-transforming RNA tumor viruses. Unlike the RNA viruses, the DNA viruses belong to several greatly different groups. Production of the so-called T antigen is a common feature of all DNA tumor viruses. This antigen occurs in all transformed cells. There are at least three virus types (papilloma virus, Epstein-Barr virus (EBV), and hepatitis B virus) contribute to the development of certain human tumors, but their contributions are less direct than in the case of infectious diseases. Only papilloma virus induces tumors directly, and most of them are benign, but papilloma virus may play a certain role in the genesis of some malignant epithelial tumors as well. Hepatitis B virus first causes liver cirrhosis, a precancerous state, the development of the tumor clone being the result of abnormal regeneration. (7 Refs) (In SWE)

OTHER RELATED STUDIES

72. HOST CELL REACTIVATION OF UV- AND X-RAY-DAMAGED HERPES SIMPLEX VIRUS BY EPSTEIN-BARR VIRUS (EBV)-TRANSFORMED LYMPHOBLASTOID CELL LINES.

Henderson EE, Long WK
Dept. Microbiology and Immunology, Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Virology; 115(2):237-248 1981

The efficacy of using an infected centers assay, employing herpes simplex virus-infected, Epstein-Barr virus-transformed lymphoblastoid cell lines (LCLs) as components, to study host cell reactivation has been explored. Herpes simplex virus Type 1 (HSV-1) was shown through the infected centers assay to have detectable but varying ability to lytically infect LCLs established from chromosomal breakage syndromes or closely related genetic disorders. The rate of HSV inactivation by UV irradiation was faster in LCLs established from Cockayne's syndrome than in normal LCLs, and faster still in LCLs established from xeroderma pigmentosum. These results indicate that Cockayne's syndrome, while having what appears to be quantitatively normal levels of UV-induced DNA repair replication, shows decreased ability to host cell reactivate UV-damaged HSV. In direct contrast, x-irradiated HSV showed identical survival when assayed on normal LCLs or LCLs established from ataxia telangiectasia showing increased sensitivity to x-irradiation as measured by colony formation. Through the infected centers assay, it has also been possible to demonstrate low levels of multiplicity reactivation of mutagen-damaged HSV in permanently proliferating LCLs. (Author abstract) (43 Refs)

73. SIMIAN VIRUS 40 AS A PROBE FOR STUDYING INDUCIBLE REPAIR FUNCTIONS IN MAMMALIAN CELLS.

Mezzina M, Gentil A, Sarasin A

Institut de Recherches Scientifiques sur le Cancer, B.P. no 8, 94802 Villejuif Cedex, France

J Supramol Struct Cell Biochem; 17(2):121-131 1981

Simian virus 40 (SV40) was used as a biological probe to examine inducible DNA repair pathways in monkey kidney cells in order to study the effect of pyrimidine dimer lesions on SV40 DNA replication, the induction of an error-prone replication process in DNA-damaged monkey cells, and the presence of recombinogenic activity in carcinogen-treated cells. Characteristics of viral replicative intermediate molecules made shortly after UV irradiation were studied in irradiated SV40-infected African green monkey cells. The tight homology between the size of newly synthesized DNA made after UV irradiation (40%), the av length of the tail measured in the same samples by electron microscopy analysis (41%), and the av distance between two pyrimidine dimers measured with the T4 endonuclease V (37%) suggested that the viral replication fork is blocked by a pyrimidine dimer leaving a single-stranded region in the opposite strand where an endonucleolytic cleavage may occur to generate the tail. Evidence for the induction of error-prone DNA replication is presented for SV40 cells in which DNA synthesis has been inhibited. An experimental protocol is proposed for the study of inducible recombination through the use of SV40 genetic markers. (36 Refs)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. O-GLYCOSIDIC CARBOHYDRATE-PEPTIDE LINKAGES OF HERPES SIMPLEX VIRUS GLYCOPROTEINS.

Olofsson S, Blomberg J, Lycke E
Dept. Virology, Inst. Medical Microbiology, Univ. Goteborg, Guldhedsgatan 10 B, S-413 46 Goteborg, Sweden
Arch Virol; 70(4):321-329 1981

Electrophoretically purified HSV-specified glycoproteins with radiolabelled carbohydrates were subjected to mild alkaline borohydride treatment (0.5 M NaOH and 0.5 M $NaBH_4$). The treatment liberated significant amounts of the labelled oli-

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gosaccharides. The latter demonstrated molecular weights of a bout 3,000 as determined by gel filtration. The glycoproteins involved probably belong to the gA/gB complex or gC. The results suggest that HSV specified glycoproteins contain oligosaccharides linked with an O-glycosidic bond to a threonine or serine residue of the polypeptide. (Author abstract) (29 Refs)

2. STRUCTURE OF ADENOVIRUS CHROMATIN.

Mirza MA, Weber J
(c/o Weber) Departement de Microbiologie, Centre Hospitalier Universitaire, Universite de Sherbrooke, Sherbrooke, P.Q. J1H 5N4, Canada
Biochim Biophys Acta; 696(1):76-86 1982

The structure of adenovirus Type 2 chromatin isolated from wild-type and ts1 virions was investigated by micrococcal nuclease digestion and electron microscopy. Partial digestion of wild-type and ts1 chromatin with micrococcal nuclease generated a multimeric DNA smear devoid of the 200 basepair nucleosome repeating pattern characteristic of cellular chromatin. However, 11 S monomer cores of 150 basepairs were detectable. The chromatin of ts1 (39 C) was more resistant to digestion by micrococcal nuclease. Two-dimensional electrophoresis of the monomer core showed that wild-type core contained protein VII while ts1 (39 C) core contained PVI and PVII. Protein V appears to be located on the variable-length intermonomer region. Crosslinking studies suggest that proteins PVII and VII exist in dimeric form within the monomer core. Electron microscopy revealed a 5.5-fold-condensed 2-micron-long beaded structure with about 200 monomer particles spaced irregularly. Based on these observations, a model for adenovirus prochromatin and chromatin is proposed that differs in important aspects from the model proposed previously. (Author abstract) (26 Refs)

3. RELATIONSHIP OF OLIGOMERIZATION TO ENZYMATIC AND DNA-BINDING PROPERTIES OF THE SV40 LARGE T ANTIGEN.

Bradley MK, Griffin JD, Livingston DM
Sidney Farber Cancer Inst., Boston, MA, 02115
Cell; 28(1):125-134 1982

Crude and highly purified SV40 large T antigen has been found to exist in forms of various sizes. Immunoreactive structures of 5.5S (80-85 kd), 7S (approx 150 kd) and 15.5S (325-340 kd) have been identified by zonal sedimentation and gel filtration. They appear to correspond to monomeric, dimeric and tetrameric species of T, respectively, and are free of detectable 55 kd NVT by specific immunoprecipitation analyses. While highly purified monomer appears relatively inactive in SV40 DNA-binding and ATPase asays, both the dimer and tetramer display these activities. By contrast, all three comigrate with casein kinase activity. These data suggest that the protein can exist as a monomer and in various homoaggregated forms. In addition, it appears that it must aggregate to be an active DNA-binding element and an ATPase. (Author abstract) (46 Refs)

4. POLYOMA VIRUS CAPSID STRUCTURE AT 22.5 A RESOLUTION.

Rayment I, Baker TS, Caspar DL, Murakami WT
Rosenstiel Basic Medical Sciences Res. Center, Brandeis Univ., Waltham, MA, 02254
Nature; 295(5845):110-115 1982

X-ray diffraction data from polyoma capsid crystals were phased by refinement of low-resolution starting models to obtain a self-consistent structural solution. The unexpected result that the hexavalent morphological unit is a pentamer shows that specificity of bonding is not conserved among the protein subunits in the icosahedrally symmetric capsid. (Author abstract) (21 Refs)

5. GASTRIN AND THE TRANSFORMING PROTEIN OF POLYOMA VIRUS HAVE EVOLVED FROM A COMMON ANCESTOR.

Baldwin GS
Melbourne Tumour Biology Unit, Melbourne, Australia
FEBS Lett; 137(1):1-5 1982

While gastrin and the transforming protein (middle T antigen) of polyoma virus appear to be superficially dissimilar molecules, a hitherto unreported structural relationship between the two proteins is presented, which supports the hypothesis that they have evolved from a common ancestor. (54 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

6. A 53-KILODALTON PROTEIN COMMON TO CHEMICALLY AND VIRALLY TRANSFORMED CELLS SHOWS EXTENSIVE SEQUENCE SIMILARITIES BETWEEN SPECIES.

Jornvall H, Luka J, Klein G, Appella E
Dept. Chemistry I, Karolinska Institutet, S-104 01 Stockholm, Sweden
Proc Natl Acad Sci USA; 79(2):287-291 1982

A heat-stable DNA-binding protein with subunits of about 53 kilodaltons (kDal) was purified from two virally transformed human cell lines (Epstein-Barr virus-positive Raji and Namalwa) and two mouse tumor cell lines (methylcholanthrene-induced Meth A sarcoma and TA3 mammary carcinoma). All four 53-kDal proteins showed closely related total amino acid compositions, similar peptide maps, and identical NH2-terminal amino acid sequences for 20 residues. These 53-kDal proteins are therefore evolutionarily highly conserved, independent of whether they originate from virally or chemically transformed cells. The NH2-terminal sequence and the protein chain as a whole are not hydrophobic; however, some unexpected residue distributions were observed. Comparisons with other proteins reveal no clear sequence similarity with known tumor antigen structures, homologous immunoglobulins, or some other proteins of known sequence. Epstein-Barr virus-determined nuclear antigen also appears to have a different NH2-terminal sequence. Thus, the results show that the 53-kDal proteins represent a unique protein type with little species variation; this finding suggests that these proteins must perform an important common function in different transformation systems. (Author abstract) (38 Refs)

7. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.

Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

Three areas of the literature on herpes simplex virus (HSV) transformation induction are reviewed: HSV-induced transformation in vitro, the contrast between HSV in vitro transformation studies and transformation induced by other DNA viruses, and mechanisms of transformation in the HSV system. Models for in vitro transformation by HSV include use of nonpermissive cells, use of virus-host range mutants, use of inactivated viruses, use of temperature-sensitive virus mutants, and use of virus DNA or restriction enzyme-digested DNA fragments. Properties of biochemically transformed cells, morphologically, and tumorigenically transformed cells, and persistence of HSV genetic material in these cells, are discussed. The major problem remaining in elucidating the role of HSV in transformation is the lack of a system in which significant levels of transformation can be obtained reproducibly. (96 Refs)

VIRUS REPLICATION AND EXPRESSION

8. EFFECTS OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON CELL PROLIFERATION AND EPSTEIN-BARR VIRUS DNA REPLICATION.

Lin JC, Smith MC, Pagano JS
Cancer Res. Center, Dept. Biochemistry and Nutrition, Sch. Medicine, Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Virology; 117(1):186-194 1982

The effect of a tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), on cell growth and replication of Epstein-Barr virus DNA in Burkitt's lymphoma cell lines and in a Burkitt somatic hybrid cell line (D98/HR-1) were studied. Following TPA treatment, cell proliferation was inhibited in all cell lines tested. The degree of inhibition of cell proliferation was greater if the cells were in a quiescent stationary phase (analogous to the G0 stage) than if the cells were in a steady-state mode of exponential growth when TPA was added. Induction of Epstein-Barr virus (EBV) DNA replication was observed only in P3HR-1 and D98/HR-1 cells, but not in Raji cells similarly exposed to TPA, as determined by cRNA-DNA hybridization with EBV-specific cRNA probe. Transient exposure (24 hr) of P3HR-1 cells to TPA followed by subsequent washing and incubation in TPA-free medium resulted in an increase (sixfold) in EBV genome copies per cell to the same level as achieved with continuous treatment; the increases in viral genome copies paralleled the increase in [3H]thymidine incorporation into EBV DNA. With transient TPA exposure, there was a 2-day lag period in cell proliferation and thereafter followed the similar kinetics of cell proliferation as those of the nontreated cells. These results indicate that transient exposure to TPA is sufficient to trigger the cells to enter the EBV replicative cycle, and the inhibition of some step in cell proliferation during the lag period may be inextricably linked to the effect of TPA in viral induction. (Author abstract) (36 Refs)

9. INDUCTION OF EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN AND DNA SYNTHESIS IN A HUMAN EPITHELIAL CELL LINE AFTER EPSTEIN-BARR VIRUS INFECTION.

Ben-Bassat H, Mitrani-Rosenbaum S, Goldblum N
Dept. Hematology, Hadassah Univ. Hosp., Jerusalem, Israel
J Virol; 41(2):703-708 1982

The association of Epstein-Barr virus (EBV) with nasopharyngeal carcinoma is supported by the presence of EBV genomes in the epithelial elements of the tumor and by elevated antibody titers to EBV-specific antigens in the patients; the levels of these titers are related to the clinical course of the disease. However, since most laboratory data suggest that EBV is a B-lymphotropic virus, it is unclear how the virus becomes associated with the epithelial elements of the nasopharynx. The purpose of the present work was to find a human model system to study this association. A human epithelial line (U) was found that could be directly infected by EBV, and viral functions, the induction of EBV nuclear antigen and cellular DNA synthesis, were demonstrated. The U line was established in 1957 by the late H J Van Kooten (Kok-Doorschodt at the University of Utrecht), and although it is no longer diploid, it exhibits density inhibition. When U cells were infected with EBV, EBV nuclear antigen was expressed in 6 to 16% of the cells, 1 and 2 days after infection with B95-8 virus, but not with the P3HR-1 strain. No evidence for virus replication was obtained; immunofluorescence staining for early antigens and virus capsid antigens gave negative results. Quantitative adsorption experiments for EBV indicated that the adsorption capacity of U cells is significant (60% of Raji cells). The present results also demonstrated that infection with the virus overcomes block(s) in cellular DNA synthesis caused by 5-fluorodeoxyuridine. The induction of DNA synthesis was determined by increased incorporation of [3H]thymidine into the cells. The highest level of isotope incorporation was observed at about 15 hr after infection and thereafter decreased. Analysis of the induced DNA indicated that it was of cellular origin. (Author abstract) (36 Refs)

10. EPSTEIN-BARR VIRUS SUSCEPTIBILITY OF B CELLS CORRELATES TO THE PRESENCE OF COMPLEMENT RECEPTORS BUT NOT SURFACE IMMUNOGLOBULINS.

Takada K, Osato T
(c/o Osato) Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan
Intervirology; 16(2):118-122 1981

Nuclear antigen (EBNA) inducibility by Epstein-Barr virus (EBV) was assessed in relation to the presence of complement (C3) receptors and surface immunoglobulins (SIg) on leukemic lymphocytes. When erythrocyte-antibody-complement complex (EAC)-positive, SIg-negative B cells were exposed to EBV, EBNA synthesis occurred with a high frequency. In contrast, no significant EBNA induc tion was evident in SIg-positive, EAC-negative B cells. Cells possessing both markers were EBV-infectable, in proportion to the frequency of EAC-rosette formation. These data seem to indicate that EBV susceptibility of human B cells is closely related to the presence of C3 receptors but not SIg. Leukemic T cells and myelogenous leukemia cells were not EBV-susceptible, although some cells were significantly positive for C3 receptors. (Author abstract) (15 Refs)

11. USE OF FLUORESCEINATED EPSTEIN-BARR VIRUS TO STUDY EPSTEIN-BARR VIRUS-LYMPHOID CELL INTERACTIONS.

Khelifa R, Menezes J
(c/o Menzes) Dept. Microbiology and Immunology, Univ. Montreal, Ste-Justine Hosp., Montreal, Quebec H3T 1C5, Canada
J Virol; 41(2):649-656 1982

As a direct approach to visualize Epstein-Barr virus (EBV) binding to its cellular receptors and to learn more on the nature of this binding, virus preparations were conjugated to fluorescein isothiocyanate and used to detect EBV receptors on lymphoid cells. Different enzymatic and chemical treatments were also applied either to the virus or to target cells or to both, and the effect of these treatments on virus binding was then examined. The results obtained show that: (i) EBV can be fluoresceinated without affecting its infectivity or cell binding ability, and the fluoresceinated virus represents an important tool to investigate the biology and nature of EBV interactions with its cellular receptors; (ii) the two virus strains (P3HR-1 and B95-8) share common receptors on Raji cells; (iii) protease treatment of EBV or target cells abrogates virus binding; (iv) EBV receptors regenerate after removal of the protease, and this regeneration is inhibited by cycloheximide or sucrose; (v) EBV particles bear concanavalin A receptors, and this lectin hinders the interaction of the virus with its cellular receptors; (vi) neuraminidase treatment, various monosaccharides, ovalbumin, and glycopeptides derived from EBV or cell surface do not inhibit virus binding. Taken together, the above data also demonstrate that some cellular and viral surface (glyco-) proteins are required for EBV binding to its targets. (Author abstract) (26 Refs)

12. ACTIVATION OF HERPES SIMPLEX VIRUS (HSV) TYPE 1 GENOME BY TEMPERATURE-SENSITIVE MUTANTS OF HSV TYPE 2.

Wigdahl BL, Isom HC, De Clercq E, Rapp F
(c/o Rapp) Dept. Microbiology and Specialized Cancer Res. Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Virology; 116(2):468-479 1982

Previous studies have demonstrated that herpes simplex viruses (HSV) Type 1 (HSV-1) and Type 2 (HSV-2) can be maintained in a repressed form in human embryo lung cells. Reducing the incubation temperature or superinfecting with a heterologous herpesvirus, human cytomegalovirus (HCMV), results in activation of virus replication. We now report that superinfection with a partially homologous herpesvirus, HSV-2, also resulted in activation of HSV-1. To minimize excessive synthesis of infectious HSV-2 while allowing virus gene expression, repressed HSV-1-infected cultures were superinfected with HSV-2 temperature-sensitive (ts) mutants (tsF3, tsB5, or tsH9). The predominant virus replicated after HSV-2 ts mutant superinfection at a nonpermissive temperature was identified as activated parental-like HSV-1 by (i) plaquing efficiency at permissive (34 C) and nonpermissive (40.5 C) temperatures, (ii) sensitivity to inhibition by the HSV-1-specific antiviral agent (E)-5-(2-bromovinyl)-2'-deoxyuridine, and (iii) restriction endonuclease cleavage analysis. In addition, the fact that superinfection with HSV-2 tsB5 or tsH9, which are unable to synthesize virus DNA and express only early virus genes at nonpermissive temperature, resulted in synthesis of virus demonstrated that HSV-2 DNA synthesis is not required for activation. This system has provided the basis for further studies concerning the regulation of HSV gene expression in human cells. (Author abstract) (31 Refs)

13. LIMITED TRANSCRIPTION OF THE HERPES SIMPLEX VIRUS GENOME WHEN LATENT IN HUMAN SENSORY GANGLIA.

Galloway DA, Fenoglio CM, McDougall JK
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Virol; 41(2):686-691 1982

Human paravertebral ganglia were examined for the presence of specific sequences of viral RNA by in situ cytological hybridization, using as probes individual fragments of herpes simplex virus Type 2 DNA. Ganglia were obtained at autopsy from 40 patients, and 14 were postive for herpes simplex virus RNA. Transcripts from the left-hand 30% of the viral genome were detected in all of the herpes simplex virus-positive cases. RNA homologous to other sequences from the L component were present less frequently, and no RNA from the S component was detected. These results argue that specific transcription of the herpes simplex virus genome occurs in latently infected human ganglion cells. (Author abstract) (24 Refs)

14. MICROSCOPIC EXAMINATION OF THE INTRACELLULAR FATE OF INFECTIOUS HERPES SIMPLEX VIRUS DNA.

Marciano-Cabral F, Cabral GA, Taylor MM, Patterson M, Farber FE

Dept. Microbiology, Medical Coll. Virginia, VCU, Box 678 - MCV Station, Richmond, VA, 23298

Intervirology; 16(2):95-105 1981

The intracellular fate of 3H-labeled exogenous herpes simplex virus Type 2 DNA following the exposure of recipient cells to selected DNA facilitators and the ultrastructural changes which ensued in transfected cultures were examined. In most cases, electron microscopic radioautography demonstrated that exogenous DNA reached the nucleus within 1 hr postinoculation. At later time periods, enlargement of nuclei and margination of chromatin were noted. Cells treated with polyornithine differed significantly from those treated with other facilitators in that large cytoplasmic accumulations of labeled material associated with electron-dense, membrane-bound bodies persisted after 1 hr postinoculation. In contrast, labeled DNA released by intact virions was detected in the nucleus as early as 20 min postinfection (pi), and progeny virus was evident by 8 hr pi. These results suggest that the efficiency of each facilitator is related to the rapidity with which exogenous DNA penetrates the recipient cell, traverses the cytoplasm, and the amount of DNA which is finally associated with the nuclear compartment. (Author abstract) (15 Refs)

15. INTERACTION OF HERPES SIMPLEX VIRUS WITH HUMAN CELL LINES AT VARIOUS STAGES OF LYMPHOID DIFFERENTIATION.

Katz E, Mitrani-Rosenbaum S, Margalith E, Ben-Bassat H

(c/o Ben-Bassat) Dept. Hematology, Hebrew Univ.-Hadassah Univ. Hosp. and Medical Sch., Jerusalem, Israel

Intervirology; 16(1):33-42 1981

The growth of herpes simplex virus (HSV) Type 1 in human lymphoid cell lines, arrested at various stages of differentiation, was studied. The synthesis of viral DNA and antigens and the production of infectious virus were followed in null, B and T leukemia-lymphoma cell lines. It was found that while 'nondifferentiated' null cells and cells differentiating along the B pathway, even at very early stages of differentiation, supported HSV growth, cell lines of T origin at all stages of differentiation were generally nonpermissive. The failure of T cells to support the growth of HSV did not result from inefficient adsorption to the host cell. However, viral DNA synthesis was not detected, and a significant reduction in the ability to synthesize HSV antigens was observed. It is suggested that the block in the growth cycle of the virus occurs at a stage after adsorption of the virion to the cells, but prior to synthesis of its DNA and proteins. (Author abstract) (22 Refs)

16. PATHWAY OF ASSEMBLY OF HERPESVIRUS CAPSIDS: AN ANALYSIS USING DNA+ TEMPERATURE-SENSITIVE MUTANTS OF PSEUDORABIES VIRUS.

Ladin BF, Ihara S, Hampl H, Ben-Porat T
(c/o Ben-Porat) Dept. Microbiology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Virology; 116(2):544-561 1982

It was reported previously that nine different DNA+ ts mutants of Pr virus were all defective in the processes leading to the cleavage of concatemeric viral DNA and to the formation of nucleocapsids. Six of these mutants were found to assemble capsids at the nonpermissive temperature; three were capsid-. In the present communication we have characterized these mutants further. Each of the mutants was rescued by one specific restriction fragment of wild type virus DNA indicating that none of these mutants is altered in more than one locus. Many of the mutants complemented one another well at a frequency indicating that they are probably mutated in different genes. Cells infected at the nonpermissive temperature (41 C) with the DNA+ mutants synthesized all the virus proteins synthesized by wild type-infected cells (as detected by PAGE) with two notable exceptions: (1) ts1-infected cells synthesized a thermolable 142K capsid protein. (2) In ts1, ts109, and tsJ (all capsid-mutants)-infected cells, detectable amounts of 35K capsid protein did not accumulate. The 35 K capsid protein is normally processed from a precursor protein, the processed protein being detectable in the nucleus of the infected cells only. In capsid- infected cells processing of the 35K protein precursor did not occur. Furthermore, accumulation in the nucleus of all capsid proteins was impaired in all the capsid-infected cells. Because at least two of the three capsid- mutants are mutated in different genes, we conclude that the processing of the 35K protein, capsid assembly, and accumulation of capsid proteins in the nuclei are interdependent events which occur only if all the proteins necessary for capsid assembly are functional. On the basis of these results, we propose that the 35K protein is processed during capsid assembly and the assembly of the proteins into capsids is required for the continued movement of capsid proteins to, and their accumulation in, the nuclei of infected cells. (Author abstract) (38 Refs)

17. ASSEMBLY OF ADENOVIRUS PENTON BASE AND FIBER.

Boudin ML, Boulanger P
(c/o Boulanger) Laboratoire de Virologie Moleculaire (U-233), Inserm, Place de Verdun, Lille, France
Virology; 116(2):589-604 1982

Human adenovirus Type 2 (H2) fiber isolated from the cellular pool of H2 wild-type (WT) soluble components was found to be capable of assembly in vitro with penton base obtained from the fiber-defective temperature-sensitive (ts) mutant H2 ts-125. This assembly occurred over a relatively broad range of pHs (5.5-9.0) and of ionic strengths (0.05-1.0). The extent of penton formation was estimated by two-dimensional immunoelectrophoresis. The legitimacy of the assembly in vitro was demonstrated by morphological, biochemical, and biological evidence. The assembly of the penton base with the fiber appeared to be a reversible reaction, with a dissociation constant KD = 2x10(-7) M, in terms of fiber molarity. This value implied a high affinity of the penton base for the fiber. Comparative digestions by carboxypeptidase of uncombined fiber and of penton base-combined fiber suggested that the recognition site for assembly involved the last 20 amino acids of the C-terminal sequence of the fiber polypeptide chain. The same analysis performed on [14C]glucosamine-labeled fiber and penton seemed to indicate that the carbohydrate units carried by the fiber were positioned too far from the C-end to be directly involved in the recognition and assembly process of the penton base with the fiber. Chimeric penton produced in vitro by incubating fiber and penton base from different adenovirus serotypes, as well as in vivo by interserotypic ts+ recombinants suggested a group specificity of the recognition site on the fiber and a likely highly conserved C-terminal amino acid sequence. Assembly of penton base and fiber in vitro resulted in a significant change in the antigenicity of the penton base-combined fiber, which was thought to reflect some three-dimensional remolding. (Author abstract) (25 Refs)

18. PERSISTENT INFECTION WITH ADENOVIRUS TYPES 5 AND 6 IN LYMPHOID CELLS FROM HUMANS AND WOOLLY MONKEYS.

Andiman WA, Miller G
Dept. Pediatrics, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
J Infect Dis; 145(1):83-88 1982

Chronic infection with adenovirus Types 5 and 6 was established in primary mononuclear leukocytes from human umbilical cord blood and in Epstein-Barr virus (EBV)-transformed B lymphocytes from human umbilical cord blood and from woolly monkey blood. Adenovirus could be recovered from cultures of primary leukocytes and of EBV-transformed lymphocytes for 2 and 3 mo, respectively, without visible alteration of cell growth. Infection in cultures of EBV-transformed lymphocytes from woolly monkey blood was obliterated by exposure to antibody, but EBV-transformed lymphocytes from human umbilical cord blood contained small amounts of virus for prolonged periods that restored infection in the culture when antibody was removed. Thus, chronic infection of lymphoid cells by some adenoviruses is maintained by at least two mechanisms: cell-to-cell spread of virus in the absence of antibody and intracellular persistence of infectious virus in the presence of antibody. (Author abstract) (18 Refs)

19. RESTRICTED EXPRESSION OF INTEGRATED PRIMATE TYPE-C VIRUS (GIBBON APE LEUKEMIA VIRUS-SIMIAN SARCOMA VIRUS) PROVIRAL DNA IN NONPRODUCTIVELY INFECTED HUMAN B LYMPHOBLASTS.

Ceccherini Nelli L, Dalla-Favera R, Markham PD, Ruscetti FW, Wong-Staal F, Gallo RC, Reitz MS
(c/o Gallo) Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Virology; 117(1):195-206 1982

Human B-lymphoblast cell lines established from peripheral blood after infection with retroviruses of the simian sarcoma/simian sarcoma associated virus (SSV/SSAV)-gibbon ape leukemia virus (GALV) group generally do not produce detectable virus, even though viral RNA and protein are expressed. We show here by Southern blot and liquid molecular hybridization experiments that most of these nonproducer cultures not producing virus contain apparently complete proviral DNA sequences which lack detectable rearrangements, indicating that restriction of virus replication is not due to obvious proviral lesions. The pro virus is often present in only a fraction of the cell population, although the proviral copy number is variable and increases during extensive tissue culture or passage through nude mice. The proviral DNA is integrated into multiple heterogeneous sites in these cells, indicating a polyclonal population. A few of these cell lines have been cloned. Clonal lines have so far originated only from cells which contain proviral DNA and express viral RNA, although they still do not produce complete or infectious virus. Southern blots show that these cells are clonal in origin and contain a complete provirus with two LTRs arranged in the normal orientation. Two viral mRNA species are expressed which are identical in size to those from virus-producing cell lines. The smaller (presumably env) mRNA, like that from virus-producing lines is a spliced transcript which contains both 5'- and 3'-derived sequences. These data strongly suggest that these cells restrict viral replication at some stage later than mRNA synthesis, possibly at the level of protein synthesis or processing. (Author abstract) (15 Refs)

20. RESTRICTED HEL-12 VIRUS INFECTION IN DE NOVO INFECTED HUMAN AND CANINE CELLS.

Black RJ, Yang JW, Panem S
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, MD, 20205
J Gen Virol; 57(part2):343-355 1981

Model systems to study restricted primate retrovirus expression were established by de novo infection of canine fetal thymus cells (CF-2Th) and superinfection of HEL-12 cells with HEL-12 virus. In the resulting CF-2Th/HEL-12V cells and HEL-12/HEL-12V cells, four sequential stages of virus infection were defined by the production of reverse transcriptase (RT)-containing particles and expression of virus antigens as detected by radioimmunoassays. Stage I cells did not synthesize virus antigens or produce RT-containing particles. Stage 2 cells synthesized virus antigen but not RT-containing particles. Stage 3 cells synthesized antigen and produced RT-containing particles, and Stage 4 cells synthesized virus antigens but no longer produced RT-containing particles. The duration of the four stage infection is 2 to 3 weeks in both cell types. Monospecific competition radioimmunoassays to detect HEL-12V p 30 or gp70 antigen showed high levels of virus antigen throughout Stages 2 to 4 of infection. Analysis of immunoprecipitates formed under conditions to detect either p30-or gp70-containing proteins in cells pulsed and pulsed-chased with [3H]leucine showed the same spectrum of virus precursor polyproteins, intermediates and mature virion components in Stage 2 to 4 cells in canine and human infections. Spent culture fluids collected from Stage 3 and Stage 4 CF-2Th/HEL-12V cells failed to reveal inhibitors of RT activity. Stage 4 CF-2Th/HEL-12V or HEL-12/HEL-12V cells labelled with [3H]uridine produced virions which incorporated [3H]uridine but did not have RT activity, suggesting that restricted infection is characterized by production of HEL-12V defective in RT activity. (Author abstract) (25 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

21. NEW EPSTEIN-BARR VIRUS VARIANTS FROM CELLULAR SUBCLONES OF P3J-HR-1 BURKITT LYMPHOMA.

Heston L, Rabson M, Brown N, Miller G
(c/o Miller) Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Nature; 295(5845):160-163 1982

Correlation between biological properties and genome structure was examined in 29 subclones of HR-1 virus, an Epstein-Barr virus (EBV) mutant that does not immortalize lymphocytes or induce lymphomas. None of the 29 clones spontaneously released EBV DNA in an amount comparable to that of the parental line. Differences in viral DNA content correlated with lower levels of viral capsid antigen (VCA) clones. Enhanced VCA expression occurred in five clones that released large amounts of DNA after treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). The subclonal viruses resembled HR-1 in lack of immortalization, cytotoxicity, and interference with transformation; unlike HR-1, they did not induce virus early antigen (EA) synthesis in Raji cells. Differences in the DNAs of nontransforming virus (HR-1 and its subclones) and two transforming EBV strains were found to involve at least six regions of the genome. HR-1 DNA differed from the DNA of cloned and transforming viruses in that it contained three or four size variants of EcoRI ABC het fragments. Possible involvement of the fragments in EA induction is noted. (22 Refs)

22. CHARACTERIZATION OF THE MAJOR EPSTEIN-BARR VIRUS-SPECIFIC RNA IN BURKITT LYMPHOMA-DERIVED CELLS.

Arrand JR, Rymo L
Imperial Cancer Res. Fund Lab., London WC2A 3PX, England
J Virol; 41(2):376-389 1982

Cytoplasmic RNA prepared from five lymphoid cell lines and a Burkitt lymphoma biopsy was radioactively labeled in vitro and hybridized to cloned EcoRI restriction endonuclease fragments of B95-8 Epstein-Barr virus DNA. The results confirmed that the most abundant cytoplasmic RNA species in such cells is specified by a small region of the genome defined by the EcoRI J fragment. Detailed mapping experiments precisely localized these transcripts within the sequence of the rightmost one-third of the EcoRI J fragment. DNA sequencing suggested that this region of the Epstein-Barr virus genome is unable to code for protein. The major early transcripts consisted of two non-polyadenylated RNA species, each about 170 nucleotides in length. They were both transcribed off the same strand of the DNA and showed significant sequence homology with each other. The coding sequences of the two small RNAs contained potential intragenic control regions for RNA polymerase III. (Author abstract) (53 Refs)

23. EVIDENCE FOR CONTROL OF HERPES SIMPLEX VIRUS MUTAGENESIS BY THE VIRAL DNA POLYMERASE.

Hall JD, Almy RE
Dept. Cellular and Developmental Biology, Univ. Arizona, Tucson, AZ, 85721
Virology; 116(2):535-543 1982

We have measured the effect of mutations associated with the DNA polymerase of herpes simplex virus Type 1 on the production of spontaneous mutants resistant to bromodeoxyuridine. Bromodeoxyuridine-resistant mutants contain mutations in the viral thymidine kinase gene. The conditional lethal mutation in strain C7, which prevents growth at 39 C and is located in the DNA polymerase gene, reduced slightly the yields of bromodeoxyuridine-resistant progeny compared to the parent virus. In contrast, a temperature-resistant derivative of C7, ts+C, produced levels of resistant progeny 11-fold greater than normal. Evidence is presented that the ts+C derivative is not a true revertant of C7, but instead contains a second site mutation which suppresses the C7 temperature-sensitive mutation. This suppressor mutation appears closely linked to the original C7 mutation. Possible mechanisms for the elevated production of bromodeoxyuridine-resistant progeny by ts+C are discussed. (Author abstract) (28 Refs)

24. PHYSICAL MAP OF THE SHORT FOLDBACK SEQUENCES OF HERPES SIMPLEX VIRUS TYPE 1 DNA.

Miller RH, Russell RJ, Hyman RW

(c/o Hyman) Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033

Virology; 117(1):70-80 1982

Short foldback sequences were found and mapped on cloned fragments of herpes simplex virus type 1 (HSV-1) DNA. Few foldbacks were within the long and short unique regions of HSV-1 DNA. However, the joint region contained numerous foldback sequences. (Author abstract) (24 Refs)

25. PROTEINS CONTAINING ONLY HALF OF THE CODING INFORMATION OF EARLY REGION 1B OF ADENOVIRUS ARE FUNCTIONAL IN HUMAN CELLS TRANSFORMED WITH THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE AND ADENOVIRUS TYPE 2 DNA.

Klessig DF, Quinlan MP, Grodzicker T

Dept. Cellular, Viral and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84132

J Virol; 41(2):423-434 1982

We introduced into tk- human 143 cells adenovirus Type 2 (Ad2) genes by transformation with a plasmid (p711) containing both Ad2 sequences and the herpes simplex virus Type 1 (HSV-1) tk gene. p711 contained approximately the left 8% of the Ad2 genome inserted in the HindIII site of pBR322, whereas the fragment of HSV-1 containing the tk gene was inserted in the BamHI site. Three tk+ cell lines were isolated after selection in HAT medium. The arrangement of viral sequences in the three transformants was analyzed by restriction endonuclease digestion and filter hybridization. All three lines contained a single insertion of Ad2 DNA which was present at approximately one copy per cell. The arrangement of Ad2 sequences in these lines was identical to that found in the linear p711 DNA used in the transformation. S1 analysis of the Ad2-specified RNA from two of these lines indicated that the early region 1a mRNA's were synthesized, though in lower amounts than found in lytic infections. These cell lines contained only the left half of early region 1b (4.6 to 11.2), which encoded the 5' portion of the 1b mRNA's. A complex pattern of 1b RNAs was made in these cell lines. Transcription of most of these RNAs began at or near the 1b promoter and proceeded through the 1b sequences into the flanking pBR322, HSV-1, or host sequences. Since many of the RNAs were terminated or spliced in the HSV-1 (anti-sense strand) or pBR322 sequences, new RNA processing sites must be used in the formation of these mRNA's. All three lines fully complemented the 1a deletion mutant Ad5 dl312. Surprisingly, these lines also permitted the growth of 1b deletion mutants (Ad5 dl313 and Ad5 dl434), although the complementation was not always complete. Presumably the new gene product(s) which contained only part of the 1b gene provided most of the essential function(s) required for viral multiplication. Alternatively, the 1b 19-kilodalton protein which was entirely encoded by the adenovirus sequences present in these cell lines was sufficient for viral growth even in the absence of the 1b 55-kilodalton protein. (Author abstract) (50 Refs)

26. PHYSICAL MAPPING OF ADENOVIRUS TYPE 2 TEMPERATURE-SENSITIVE MUTATIONS BY RESTRICTION ENDONUCLEASE ANALYSIS OF INTERSEROTYPIC RECOMBINANTS.

D'Halluin JC, Cousin C, Boulanger P

(c/o Boulanger) Lab. Virologie Moleculaire, Institut Natl. de la Sante et de la Recherche Medicale, 59045 Lille Cedex, France

J Virol; 41(2):401-413 1982

The genome structures of about 100 interserotypic ts recombinants produced in crosses between human adenovirus Type 2 (H2) and 5 (H5) temperature-sensitive mutants were analyzed by cleavage with restriction endonucleases to determine the map coordinates of the following temperature-sensitive mutants: penton base plus fiber-defective H2 ts103,-104, and-136, assembly-defective H2 ts112, fiber-defective H2 ts125, hexon-defective H2 ts118 and-121, and DNA-negative H2 ts111. H5 ts1 (100 K defective), H5 ts36 (DNA negative), H5 ts125 (mutated in the early 72,000-dalton protein), H5 ts22 (fiber defective), H5 ts58 (IIIa defective), and H5 ts18 and-19 were used as one of the parents. The physical locations of the H2 temperature-sensitive mutations thus defined are discussed in relation to the genetic map, the biological function altered, and the positions of the structural genes on the genome. (Author abstract) (38 Refs)

27. DNA SEQUENCES AFFECTING SPECIFIC INITIATION OF TRANSCRIPTION IN VITRO FROM THE E III PROMOTER OF ADENOVIRUS 2.

Lee DC, Roeder RG, Wold WS

Dept. Pharmacology SJ-30, Univ. Washington, Seattle, WA, 98195

Proc Natl Acad Sci USA; 79(1):41-45 1982

We have identified those sequences affecting the level of specific initiation of transcription in vitro from the EIII promoter of adenovirus 2. Mutants containing deletions in and around the initiation sites were constructed in cloned viral DNA fragments and assayed for their ability to initiate transcription in vitro. Three classes of mutants were studied with deletions in the following regions:-38 to-268,-21 to-71 (which includes the T-A-T-A-A box), and-29 through the cap sites (+1 and +3). Deletions that remove some or all of the area from-28 to several nucleotides downstream from the cap sites essentially abolished specific transcription. Small deletions in the region-30 to-41 reduced transcription to approx 60% of wild type; larger deletions in the region-35 to-268 reduced transcription to 30-40% of wild type. Deletions beginning from approximately +10 to +25 and extending further downstream reduced transcription to 20-40% of wild type, whereas a deletion beginning at +31 had little or no effect. Our results suggest that the region including the T-A-T-A-A box and extending to the area immediately beyond the cap sites is essential for specific transcription in vitro from the EIII promoter. However, sequences upstream from the T-A-T-A-A box and those downstream from the cap sites appear to significantly modulate the levels of transcription. (Author abstract) (26 Refs)

28. TRYPTIC AND CHYMOTRYPTIC METHIONINE PEPTIDE ANALYSIS OF THE IN VITRO TRANSLATION PRODUCTS SPECIFIED BY THE TRANSFORMING REGION OF ADENOVIRUS TYPE 2.

Halbert DN, Raskas HJ
Dept. Microbiology, Health Sciences Center, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Virology; 116(2):406-418 1982

Early region 1 (E1) cytoplasmic RNAs of adenovirus Type 2 were translated in vitro. Structural relationships between these proteins were then established by tryptic and chymotryptic digestion and two-dimensional peptide mapping. This analysis also allowed a direct comparison of these proteins with polypeptides isolated from early infected cell extracts and previously assigned to E1 by indirect means. E1a (0-4.5%) RNA encodes five proteins in vitro: 35K, 41K, 47K and 53K at early times, and a 28K protein at later times in infection. These five proteins are all highly related by peptide mapping analysis, and are also related to a group of four proteins isolated from cell extracts prepared early in infection. E1b (4.5-11.0%) early RNA encodes 52K and one or more 15K proteins in vitro. The 52K protein shares tryptic peptides with a 53K immunoprecipitated T antigen. A 15K protein shares some peptides with the 52K protein and with several proteins isolated from infected cells. At intermediate to late times, E1b RNA encodes a 12K protein that corresponds to the virion structural polypeptide IX. These data also permit the correlation of E1 proteins synthesized in vitro with the polypeptides predicted by E1 sequence analysis. (Author abstract) (45 Refs)

29. RESOLVING THE FUNCTIONS OF OVERLAPPING VIRAL GENES BY SITE-SPECIFIC MUTAGENESIS AT A MRNA SPLICE SITE.

Montell C, Fisher EF, Caruthers MH, Berk AJ
Dept. Microbiology, Univ. California, Los Angeles, CA, 90024
Nature; 295(5848):380-384 1982

Early region IA of human adenoviruses encodes a function required for normal induction of early viral genes and virus-induced cell transformation. The region is expressed at early times as two overlapping spliced mRNAs, 12S and 13S, which encode closely related proteins. To distinguish between the functions of these proteins, a single T to G transversion was constructed which prevents splicing of the 12S mRNA. This transversion, in the second base of the 12S mRNA intron, does not alter the protein encoded by the 13 mRNA due to degeneracy in the genetic code. Studies with this mutant demonstrated that only the 13S mRNA encodes the regulatory protein required for normal early gene expression. (Author abstract) (47 Refs)

30. ADENO-ASSOCIATED VIRUS RNA TRANSCRIPTION IN VIVO.

Marcus CJ, Laughlin CA, Carter BJ
Lab. Experimental Pathology, Natl. Inst. Arthritis, Diabetes, Digestive and Kidney Diseases, NIH, 9000 Rockville Pike,, Bethesda, MD, 26205
Eur J Biochem; 121(1):147-154 1981

We have studied RNA transcripts of the defective parvovirus, adeno-associated virus (AAV) present in poly-(A)rich and poly-(A)free fractions of nuclear and cytoplasmic RNA prepared from cells infected together with a helper adenovirus. Cytoplasmic poly-(A)rich RNA contains three overlapping spliced AAV RNAs having sizes of 3.9 x 10(3), 3.3 x 10(3) and 2.3 x 10(3) base respectively. The nuclear precursors of the RNAs appear to be the coterminal unspliced poly(A)-rich RNAs containing 4.2 x 10(3), 3.6 x 10(3) and 2.6 x 10(3) bases respectively. These unspliced RNAs were also found in the cytoplasm. The nuclear poly(A)-free RNA contained a heterogenous population of AAV RNAs that were generally smaller than 2.3 x 10(3) bases. In addition, the Hirt pellet fraction of the nuclear RNA contained two discrete AAV poly(A)-free RNAs having sizes of 2.5 x 10(3) and 2.8 x 10(3) bases. The 4.2 x 10(3) and 3.6 x 10(3)-base unspliced RNAs are more abundant than the coterminal 3.9 x 10(3) and 3.3 x 10(3)-base spliced RNAs whereas the 2.3 x 10(3)-base spliced RNA is much more abundant than the 2.6 x 10(3)-base unspliced RNA. Thus, the cytoplasmic abundance of the AAV spliced RNAs appears to be controlled in part by the post-transcriptional events of splicing or message stability. We also analyzed the effects of AAV defective-interfering genomes upon AAV transcription. These studies showed that when synthesis of standard AAV genomes was inhibited more than 10-fold by defective-interfering genomes there was no significant effect on the types or amounts of AAV RNA transcripts which accumulated. These observations indicate that interference by defective-interfering genomes occurs mostly at the level of DNA replication rather than transcription. (Author abstract) (24 Refs)

31. SPECIFIC INTERACTION OF THE SV40 T ANTIGEN-CELLULAR P53 PROTEIN COMPLEX WITH SV40 DNA.

Reich NC, Levine AJ
(c/o Levine) Dept. Microbiology, State Univ. New York Stony Brook, Sch. Medicine, Stony Brook, NY, 11794
Virology; 117(1):286-290 1982

Three forms of the simian virus 40 (SV40) large tumor antigen (T antigen), free T antigen from infected monkey cells, T antigen-p53 complex from virus-infected mouse cells, and T antigen-p53 complex from SV40-transformed mouse cells, were examined for their abilities to bind specifically to SV40 DNA. Employing an immunoassay that detected T antigen and/or p53 protein bound to restriction fragments of viral DNA, it was shown that all three of these forms of SV40 T antigen bind preferentially to the restriction fragment of SV40 DNA containing the nucleotide sequence at the origin of viral DNA replication. Free p53 protein alone failed to bind to SV40 DNA in this assay. These results indicate that the SV40 T antigen-p53 protein complex displays the same SV40 DNA binding specificity as free T antigen obtained from a productive infection. (Author abstract) (24 Refs)

32. TERRITORIAL LIMITS AND FUNCTIONAL ANATOMY OF THE SIMIAN VIRUS 40 REPLICATION ORIGIN.

Bergsma DJ, Olive DM, Hartzell SW, Subramanian KN
Dept. Microbiology and Immunology, Univ. Illinois Medical Center, Chicago, IL, 60612
Proc Natl Acad Sci USA; 79(2):381-385 1982

The region at and near the simian virus 40 (SV40) DNA replication origin contains a series of palindromes, a 17-base pair (bp) A+T-rich sequence, three copies of a 21-bp repeat, and two copies of a 72-bp repeat. We have constructed a series of recombinant plasmids containing sequential deletions at the region of SV40 DNA replication origin starting from the end near the repeats. These deletions were introduced by using in vitro and in vivo techniques. The relative replication efficiency of these recombinant plasmids were directly assayed in COS-1 monkey kidney cells capable of providing the tumor antigen necessary for the replication of these molecules. Recombinants lacking both copies of the 72-bp repeat did not exhibit any reduction in replication efficiency. Recombinants lacking the 21-bp repeats showed decreased replication efficiency; the reduction in replication efficiency was proportional to the number of copies of the 21-bp repeat deleted in these recombinants. A recombinant retaining the palindromes at the region of origin of SV40 DNA replication but lacking the A+T-rich sequence and the repeats failed to replicate. Based on these results, the SV40 DNA replication origin is subdivided into two regions, and their boundaries are defined. One of these two regions, and their boundaries are defined. One of these two regions is a core region containing the 17-bp, 15-bp, and 27-bp palindromes and, quite likely, the 17-bp A+T-rich sequence which are necessary for replication. The other is an auxiliary region that consists of the 21-bp repeats and has a dose-dependent enhancement effect on replication efficiency. (Author abstract) (34 Refs)

33. INITIATION AND REGULATION OF SIMIAN VIRUS 40 EARLY TRANSCRIPTION IN VITRO.

Lebowitz P, Ghosh PK
Dept. Internal Medicine, Yale Medical Sch., New Haven, CT, 06510
J Virol; 41(2):449-461 1982

We have studied initiation and regulation of early transcription of simian virus (SV40) DNA in vitro by eucaryotic RNA polymerase II, using both a crude HeLa cell extract and a partially purified calf thymus polymerase supplemented with a HeLa cell S100 fraction. Analysis of initiation sites by primer-directed cDNA synthesis and sequencing of cDNA's has revealed that early transcription is initiated at a multiplicity of sites corresponding to the 5' termini of early viral mRNA's. The pattern of in vitro initiation closely resembles the pattern of 5' termini of early mRNA's late in the lytic cycle, with principal initiations between residues 5184 to 5194, upstream from the early Hogness-Goldberg (TATA) sequence, and at residue 5123, well downstream from this sequence. In vitro transcription is initiated to a lesser extent at sites between residues 5150 and 5155, the principal 5' termini of early mRNA's in transformed cells and early in lytic infection, located 21 to 26 nucleotides downstream from the TATA sequence. Initiation occurs at identical sites and with similar efficiencies on form I and linearized DNA templates. There are minor differences in the efficiency of initiation at specific sites by the two transcriptional systems. Studies using a DNA template cleaved just downstream from the TATA sequence and a second template cleaved through a pair of 72-base-pair tandem repeats starting 87 nucleotides upstream from the TATA sequence have revealed that neither the TATA sequence nor the repeats are essential for early transcription in vitro. However, removal of the TATA and upstream sequences shifts initiation of transcription principally to the residue 5123 site. Comparison of the relative efficiencies of transcription on intact wild-type DNA, the two cleaved DNAs, and DNA from a deletion mutant suggests that all or most of the sequences constituting an early promoter lie within the genomic region 60-70 to 140 nucleotides upstream from the principal 5 ' termini of the early mRNA's. (Author abstract) (43 Refs)

34. SECONDARY STRUCTURE MODEL FOR THE COMPLETE SIMIAN VIRUS 40 LATE PRECURSOR MRNA.

Nussinov R, Tinoco I, Jacobson AB
Dept. Chemistry, Univ. California at Berkeley, Berkeley, CA, 94720
Nucleic Acids Res; 10(1):351-363 1982

Structures for all sequences containing less than 1,790 nucleotides in the 2,600 nucleotide late region of the SV40 virus have been computed and saved on magnetic tape. Previously the longest sequence whose secondary structure was calculated in a single computer run contained 950 nucleotides. In the past, analysis of long molecules required numerous repeated, partially overlapping computations on much shorter segments. The structure obtained for the late half of the SV40 is Y-shaped with two unequal arms. It has 52 short hairpins. Two long range interactions between nucleotides near 650 and 1,350 and between 1,450 and 2,450 appear to play an important role. The first is within the 16S intron; the second is in the 3' exon. The 5' and 3' ends of the molecule are close to each other and are found in the major elongated stem in the vicinity of the fork. (Author abstract) (30 Refs)

35. HIGH FREQUENCY OF GENE TRANSFER AFTER FUSION BETWEEN BACTERIA AND EUKARYOTIC CELLS.

Rassoulzadegan M, Binetruy B, Cuzin F

Centre de Biochimie du CNRS, Universite de Nice, Parc Valrose, 06034 Nice, France

Nature; 295(5846):257-259 1982

The possibility of producing stable transformants using eukaryotic simian virus 40 (SV40) genes carried in a bacterial plasmid was studied. SV40 genes can be directly transferred into mammalian cells in culture; after polyethylene glycol-induced fusion with bacterial protoplasts, a fraction of the recipient cells yields infectious virus. Cells from Escherichia coli strain 1106 carrying one of the plasmids were grown to a density of 2 x 10(8) cells/ml. Transformed foci were observed after fusion of FR3T3 rat cells with bacteria carrying plasmid pPY-1. Efficiency of focus formation after transfer of either polyoma virus or SV40 early genes was at least equal to focus transformation observed after infection with virions. At high ratios of bacteria/recipient cells, all the cells expressed the early viral proteins 48 hr after fusion. Under optimal conditions, transfer by fusion appeared to be 10-to 20-fold more efficient than DNA transfection by the Ca++ co-precipitation technique for introduction of foreign genes into eukaryotic recipients. A systematic analysis of the parameters involved indicated that the extent of lysosome treatment was critical. The chloramphenicol amplification step seems to be essential; in several cases where the step was omitted, using either pBR322 or pAT153 plasmid, no transformants were produced after fusion. Another important parameter that must be considered is the choice of bacterial strain. (12 Refs)

36. CHARACTERISTICS OF BK PAPOVAVIRUS DNA PREPARED DIRECTLY FROM HUMAN URINE.

Mew RT, Lecatsas G, Prozesky OW, Harley EH

(c/o Harley) Dept. Chemical Pathology, Univ. Cape Town Medical Sch., Observatory 7925, South Africa

Intervirology; 16(1):14-19 1981

DNA was prepared directly from preparations of papovavirus excreted in the urine of two patients on immunosuppressive therapy, without preliminary amplification in cell cultures. EcoRI, BamHI, and HindIII restriction patterns were typical of BK virus DNA and were identical for the two isolates. However, there were significant differences in the sizes of the HindIII fragments when compared with those of standard cell-culture-adapted BK virus strains. (Author abstract) (13 Refs)

37. PRIMATE ORIGIN OF THE CELL-DERIVED SEQUENCES OF SIMIAN SARCOMA VIRUS.

Robbins KC, Hill RL, Aaronson SA
Lab. Cellular and Molecular Biology, Natl. Cancer Inst., Bethesda, MD, 20205
J Virol; 41(2):721-725 1982

We sought to identify the species of origin of the cell-derived (sis) sequences of simian sarcoma virus. A molecular clone comprised of sis DNA detected related nucleotide sequences at low copy numbers in normal cellular DNAs of species as diverse as humans and quail. The extent of hybridization and degree of base-pair matching with sis DNA were greatest with New World primate DNAs. The thermal denaturation curve midpoints of hybrids formed between sis and woolly monkey DNAs were indistinguishable from homologous sis DNA hybrids, establishing the woolly monkey (Lagothrix spp) as the source of sis sequences. In comparative studies, sis was shown to be more conserved among mammalian species than unique-sequence woolly monkey cellular DNA. There was no detectable homology between cis and the cell-derived sequences of other fibroblast-transforming retroviruses. These findings indicate that sis is likely to be a unique onc gene among transforming retroviruses. (Author abstract) (35 Refs)

38. DELETIONS OF SPECIFIC REGIONS OF THE SIMIAN SARCOMA-ASSOCIATED VIRUS GENOME ARE FOUND IN DEFECTIVE VIRUSES AND IN THE SIMIAN SARCOMA VIRUS.

Gelmann EP, Petri E, Cetta A, Wong-Staal F
Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
J Virol; 41(2):593-604 1982

Extrachromosomal DNA was isolated from tissue culture cells that were acutely infected with simian sarcoma virus (SSV) and its associated helper (simian sarcoma-associated virus [SSAV]). Two sizes of closed circular viral genomic DNA intermediates were isolated, cleaved at the single EcoRI site, and ligated to the Charon 21A phage lambda vector. Cloned molecules of the larger size all represented the full-length (9.0-kilobase [kb]) SSAV molecule. A heterogeneous group of clones was derived from the smaller DNA circles. These included the SSV genome and SSAV deletion mutants. When two SSV clones were compared with the helper, they contained the following three characteristic deletions: (i) a 250-base pair deletion in the gag gene about 1.0 kb from the 5' end of the genome; (ii) a 1.85-kb deletion in the pol gene; and (iii) a 1.9-kb deletion at the 3' end, which included part of the env gene. This latter deletion was the site of the onc gene substitution. Six other clones of the smaller molecules represented the following variants of the SSAV genome: (i) two clones of the entire genome containing only one long terminal repeat unit; (ii) one clone with the 1.85-kb deletion of the pol gene observed in SSSV; and (iii) three clones having a deletion of the 3' end of the SSAV genome. In each of the latter clones, the 5' border of the deletion was indistinguishable from the 5' border of the onc substitution in SSV. The fidelity of genetic deletions observed suggested that certain regions of the SSAV genome were deleted at a high frequency. In certain cases, these deletions may have been accompanied by a substitution of cellular sequences to generate SSV. (Author abstract) (27 Refs)

39. CELLULAR GENES ANALOGOUS TO RETROVIRAL ONC GENES ARE TRANSCRIBED IN HUMAN TUMOUR CELLS.

Eva A, Robbins KC, Andersen PR, Srinivasan A, Tronick SR, Reddy P, Ellmore NW, Galen AT, Lautenberger JA, Papas TS, Westin EH, Wong-Staal F, Gallo RC, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 295(5845):116-119 1982

Polyadenylated RNAs of certain human tumor cell lines are shown to contain transcripts related to the cell-derived transforming onc genes of molecularly cloned primate, murine or avian transforming retrovirus genomes. Thus, analogues of retroviral transforming genes are both present and frequently expressed in human neoplastic cells. (Author abstract) (52 Refs)

40. ORGANIZATION OF TYPE C VIRAL DNA SEQUENCES ENDOGENOUS TO BABOONS: ANALYSIS WITH CLONED VIRAL DNA.

Battula N, Hager GL, Todaro GJ
Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20205
J Virol; 41(2):583-592 1982

Unintegrated linear and circular forms of baboon endogenous Type C virus M7 DNA were prepared from M7-infected cells by chromatography on hydroxyapatite columns, and the circular DNAs were purified in cesium chloride-ethidium bromide equilibrium density gradients. The circular DNAs were linearized by digestion with EcoRI, which had a unique site on the viral DNA. The linearized DNA was then inserted into lambdagtWES-lambdaB at the EcoRI site and cloned in an approved EK2 host. Molecularly cloned full-length M7 DNA was restricted with BamHI, and the resulting five subgenomic fragments were then subcloned individually in plasmid pBR322. The organization and sites of integration of the approx 100 copies of M7 DNA sequences endogenous to baboons were investigated by digesting the DNA with restriction enzymes and identifying the virus-specific fragments by hybridization to labeled probes made by using the molecularly cloned full-length and subgenomic fragments of the viral DNA. We found that most of the endogenous sequences had sizes and organizations similar to those of the unintegrated viral DNA and therefore approx similar to the RNA of the infectious virus. A few of the multiple sequences had deletions in the 3' end (envelope region), and some of the sequences either lacked or contained modified BamHI restriction sites on the 5' end of the viral DNA. The endogenous viral DNA sequences were nontandera, uninterrupted, and colinear with the DNA of the infectious virus, and they were integrated at different sites in the baboon DNA, like the M7 proviral DNA sequences acquired upon infection. (Author abstract) (41 Refs)

41. RESTRICTION MAPPING OF CLONED BABOON ENDOGENOUS VIRUS DNA AND NUCLEOTIDE SEQUENCES OF THE LONG TERMINAL REPEATS (MEETING ABSTRACT).

Takano T, Tamura T, Noda M
Department of Microbiology, Keio University School of Medicine, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Closed circular DNAs of baboon endogenous virus M7 were isolated from the Hirt's supernatant fraction of early infected human rhabdomyosarcoma cells. A204. The circular viral DNAs were cloned in bacteriophage lambda, Charon28. Seventeen independent clones were isolated and analyzed by restriction mapping. Nine clones carried a viral sequence of 8.6 kilo-base pairs (kb) with two tandem repeats of 0.6 kb, which correspond to the large circular form of the unintegrated M7 DNA. Eight other clones had the viral insert of 8.0 kb, ie, the small circular form, and were deleted in one of the repeated sequences. One of the recombinants of the large circular M7 DNA had an inversion of 2.5 kb. One of the ends of the inversion was near the terminus of the repeated sequences and the other end in the gag gene region. The inversion seems to be casued by integration of a viral DNA within itself during early periods of infection. The repeated sequences were subcloned in bacterial plasmid pBR322 and analyzed the nucleotide sequences. A poly (A) signal (5'AATAAA) was detected at 11 bases upstream of a Hogness box (5'TATAAAA) in the repeated sequences, ie, the long terminal repeats. Findings for the functions of the long terminal repeats will be presented at the meeting. (no Refs)

IMMUNOLOGICAL STUDIES

42. EFFECT OF DIFFERENT EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS (EBNA, EA, AND VCA) ON THE LEUKOCYTE MIGRATION OF HEALTHY DONORS AND PATIENTS WITH INFECTIOUS MONONUCLEOSIS AND CERTAIN IMMUNODEFICIENCIES.

Szigeti R, Masucci MG, Henle W, Henle G, Purtilo D, Klein G

Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden

Clin Immunol Immunopathol; 22(1):128-138 1982

Leukocytes from healthy Epstein-Barr virus (EBV)-seropositive (SP) subjects show significant migration inhibition (LMI) with EBNA (EBV-determined nuclear antigen)-containing extracts derived from nonproducer, EBV-genome-carrying cells, or presented in the form of partially purified EBNA-preparations. Additional EBV antigens, EA and VCA, presented in the form of induced cell extracts do not add any measurable increase to their response. Leukocytes from acute infectious mononucleosis (IM) patients, on the other hand, do not respond to EBNA, but they show a good response to induced EA- or EA and VCA-containing cell extracts. This is in accordance with known differences in EBV-antibody pattern in healthy SPs as contrasted to acute IM patients. Leukocytes from chronic mononucleosis patients resemble those from acute IM patients in their preferential EA/VCA and deficient EBNA response in the LMI test. Cells from four X-linked lymphoproliferative disease (XLP) patients showed complete absence of reactivity to PHA and to EBV antigens in the LMI test, showing a general defect in cell-mediated immune responses. Leukocytes from a group of patients with lymphoproliferative malignancies in remission and elevated EBV-antibody titers showed a variety of responses, resembling normal SP donors, or IM patients, or showing a complete unresponsiveness in the LMI test. (Author abstract) (41 Refs)

43. ANTICOMPLEMENT IMMUNOENZYMATIC METHOD OF DETECTING EPSTEIN-BARR NUCLEAR ANTIGEN IN NASOPHARYNGEAL CARCINOMA CELLS IN NORMAL EPITHELIAL CELLS.

Zeng Y, Shen S, Pi G, Ma J, Zhang Q, Zhao M, Dong H

Inst. Virology, Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Chin Med J [Engl]; 94(10):663-668 1981

Epstein-Barr nuclear antigen (EBNA) was tested for by both anticomplement immunofluorescence and anticomplement immunoenzymatic (ACIE) methods in nasopharyngeal cells from 79 patients with nasopharyngeal carcinoma (NPC), cells from 66 patients with suspected NPC, cells from head and neck tumors other than NPC (18), and cells from the nasopharyngeal mucosa of 3-8 mo old dead fetuses (21). ACIE studies of exfoliated cells indicated NPC in 79 cases, of which 62 were also NPC-positive upon histologic and cytologic examination, 10 were NPC-positive by histologic examination only, and 7 were NPC-positive by cytologic examination only. Nine of the suspected cases were NPC-positive by the ACIE method, but were negative upon cytologic or histologic examination. None of the head neck tumor smears or fetal mucosa cells were NPC-positive by any method used. The findings of EBNA in carcinoma cells, hyperplastic epithelial (HE) cells, and ciliated columnar epithelial (CCE) cells of NPC patients, and in HE cells and CCE cells of normal individuals, but with less found in squamous epithelial cells, suggest that Epstein-Barr virus infects normal epithelial cells first, especially CCE cells, integrating its DNA into cellular DNA. (11 Refs)

44. HISTOLOGICAL TYPES OF NASOPHARYNGEAL CARCINOMA AS COMPARED TO EBV SEROLOGY.

Krueger GR, Kottaridis SD, Wolf H, Ablashi DV, Sesterhenn K, Bertram G

Immunopathology Labs., Univ. Cologne, Joseph-Stelzmann-Strasse 9, 5000 Koln 41, W. Germany

Anticancer Res; 1(4):187-194 1981

One hundred and thirteen cases of nasopharyngeal carcinoma were classified according to the World Health Organization (WHO)-, French-, and Cologne classification systems and the various histologically defined types were correlated with data on Epstein-Barr virus (EBV) serology (EA, VCA, EBNA, CF, and IgA-VCA). Significantly elevated titers of anti-EBV antibodies were found primarily in undifferentiated carcinomas with or without lymphoid infiltration and in nonkeratinizing carcinomas (NKC) with lymphocytic infiltration. The classification systems used, when combined with clinical data, correlated well with results of serological investigations for EBV induced antibodies, and may help identify the primary tumor site. Of the three systems studied, the French system was the simplest and correlated well with serologic data. An undifferentiated carcinoma of the 'nasopharyngeal type' could be misdiagnosed if serologic studies were not performed. The WHO classification had limited reproducibility for differentiating NKC from undifferentiated carcinomas. NKC were heterogeneous with respect to their EBV related pathogenesis. The Cologne modification of the WHO system may eliminate some of these problems of the WHO system. It is recommended that any of the two proposed classification systems be used in parallel and together with adequate serological studies. (29 Refs)

45. CORRELATION BETWEEN MIXED LYMPHOCYTE CULTURES AND ANTI-EPSTEIN BARR VIRUS (EBV) ANTIBODIES IN HODGKIN'S DISEASE AND NON HODGKIN LYMPHOMA PATIENTS.

Sasiain MC, Fejes M, Ares BR, Brezavscek D, Bachmann AE
Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina
Biomedicine [Express]; 35(5):153-156 1981

Cellular and humoral immunity was examined in Hodgkin's disease and non Hodgkin lymphoma (33) patients and compared with a normal group. Mixed lymphocyte cultures (MLC) were used as a parameter for cell mediated immunity and anti-Epstein Barr virus (EBV) antibodies for specific humoral immunity. High stimulation indices coincided with low anti-VCA and anti-EBNA titers in the control group (r =-0.343). This negative correlation was not found in non Hodgkin lymphomas and was substantially lower (r =-0.142) in Hodgkin's disease. The alterations in immunoregulatory mechanisms in these patients are discussed. (Author abstract) (29 Refs)

46. NASOPHARYNGEAL CARCINOMA IN AMERICAN CHILDREN: EPSTEIN-BARR VIRUS-SPECIFIC ANTIBODY TITERS AND PROGNOSIS.

Naegele RF, Champion J, Murphy S, Henle G, Henle W
Div. Infectious Diseases, St. Jude Children's Res. Hosp., Memphis, TN
Int J Cancer; 29(2):209-212 1982

Seven American juvenile patients with undifferentiated or nonkeratinizing nasopharyngeal carcinoma (NPC) were examined serially for Epstein-Barr virus (EBV)-specific antibody spectra and titers in sera. At diagnosis, all showed antibody patterns characteristic of NPC: ie, high titers of IgG antibodies to viral capsid antigen (VCA) and to the diffuse (D) component of the early antigen complex. Six patients had IgA antibodies to VCA, and four to the D component. In the patients who responded to therapy with complete and maintained remissions, the IgG antibodies to D and the IgA antibodies to VCA and D decreased to undetectable levels within 12 to 30 mo. By contrast, of the four patients who responded only transiently to therapy, three showed substantial increases and one continuously high titers of IgG anti-D and IgA anti-VCA. The increases in antibody titers preceded clinical recognition of recurrent tumors by 1 to 6 mo. Three of these patients have died and the fourth is alive with disease. These data indicate that American juvenile NPC does not differ from the adult disease observed anywhere in the world. They reaffirm the potential usefulness of EBV-specific serology in the diagnosis and prognosis of NPC and the monitoring of patients following therapy. (Author abstract) (35 Refs)

47. IMPROVED IMMUNOFLUORESCENCE ANTIGENS FOR DETECTION OF IMMUNOGLOBULIN M ANTIBODIES TO EPSTEIN-BARR VIRAL CAPSID ANTIGEN AND ANTIBODIES TO EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN.

Gallo D, Walen KH, Riggs JL
Viral and Rickettsial Disease Lab., California Dept. Health Services, Berkley, CA, 94704
J Clin Microbiol; 15(2):243-248 1982

Epstein-Barr viral capsid antigen (VCA) and nuclear antigen produced by modified procedures were evaluated for use in measuring VCA IgM and Epstein-Barr virus (EBV) nuclear antigen antibody responses in sera from patients with EBV infection. VCA production was stimulated with a phorbol ester, and the EBV nuclear antigen (EBNA) cells were fixed in suspensions to eliminate loss of antigen during the drying process. Approx 70% of the tumor-promoter agent-stimulated P3HR-1 cells fluoresced when reacted with VCA-IgM- or VCA-IgG-positive sera. In the anticomplement immunofluorescence test for EBNA antibody, 100% of the cells (except the dead ones) in every smear tested showed dense nuclear fluorescence with positive sera. The improved antigen preparations were evaluated in tests on 122 sera. Twenty patients possessed antibody patterns consistent with recent EBV infection. Fifteen patients showed VCA-IgM antibody and no antibody to EBNA; both IgM and EBNA antibodies were present in later specimens taken form five patients. Patients examined in the study were heterophil negative and all were diagnostic problem cases. Patients presenting with lymphatic disease who are heterophil negative and for whom other infections have been ruled out are diagnostic problems for the clinician, especially when lymphoma is a possibility. Reliable serological tests for EBV should be helpful for studying these problem cases. (18 Refs)

48. T CELL-MEDIATED IMMUNOREGULATION OF EPSTEIN BARR VIRUS- (EBV) INDUCED B LYMPHOCYTE ACTIVATION IN EBV-SEROPOSITIVE AND EBV-SERONEGATIVE INDIVIDUALS.

Tosato G, Magrath IT, Blaese RM

Metaboism Branch, NIH, Building 10, Room 4N108, Bethesda, MD, 20205

J Immunol; 128(2):575-579 1982

Infection with Epstein Barr virus (EBV) is accompanied by seroconversion and life-long persistence of the virus in B lymphocytes. During acute EBV-induced infectious mononucleosis, suppressor T cells become activated, which may provide an additional mechanism of host defense against the causatived agent. When cultures of lymphocytes from normal adults seropositive for EBV were stimulated with the B95-8 strain of EBV, purified B cells produced increasingly higher numbers of immunoglobulin- (Ig) secreting cells, whereas in co-cultures of autologous B and T cells a profound suppressor T cell activity inhibited further B cell activation after 10 to 12 days in culture. No such T cell-mediated inhibitory effect was seen in cultures of lymphocytes obtained from normal adults seronegative for EBV, indicating a correlation between the suppressor effect with evidence of prior immunity to this virus. The T cell-mediated suppression in patients with infectious mononucleosis is characterized by an early-acting inhibitory effect on B cell differentiation that is not specific in that all polyclonal B cell activators are inhibited, whereas in EBV-seropositive normal subjects suppression is delayed in time and affects only EBV-activated cultures. These data indicate that after infection with EBV, immunoregulatory T cells are generated that are capable of inhibiting further EBV-induced activation of autologous B cells and thus may provide an additional unique mechanism of host defense against persisting EBV-infected B cells. (Author abstract) (35 Refs)

49. ABNORMAL ANTI-EPSTEIN BARR VIRUS ANTIBODIES IN CARRIERS OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME AND IN FEMALES AT RISK.

Sakamoto K, Seeley JK, Lindsten T, Sexton J, Yetz J, Ballow M, Purtilo DT

(c/o Purtilo) Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105

J Immunol; 128(2):904-907 1982

The asymptomatic hemizygous female carriers of the x-linked lymphoproliferative syndrome (XLP) have abnormal antibody responses to EBV. This suggests partial expression of the defect that leads to EBV-provoked life-threatening diseases in their affected sons. EBV specific antibodies were measured in 65 serum samples of 12 obligate carrier females and 7 of their daughters (females at risk) during periods ranging from 1 to 5 yr. Abnormal qualitative antiviral capsid antigen (VCA) IgG titers were nearly fourfold higher than normal controls, two carriers had persistent IgM anti-VCA antibody, two-thirds had persistent IgA anti-VCA antibody, and half of the women had titers to early antigen (EA). Five of seven females exhibited a similar persistent pattern. In contrast, none of the unaffected family members nor 23 normal controls expressed IgA or IgM titers to VCA even with high exposure to the virus, and anti-EA was detected in only one control. Therefore, these findings may prove useful for detecting carriers of the syndrome. Abnormal anti-EBV titers similar to the carrier pattern have been reported in patients and other immunosuppressed individuals, and are indicative of active viral infection. (Author abstract) (31 Refs)

50. EFFECT OF MONOCLONAL ANTIBODIES ON LIMITED PROTEOLYSIS OF NATIVE GLYCOPROTEIN GD OF HERPES SIMPLEX VIRUS TYPE 1.

Eisenberg RJ, Long D, Pereira L, Hampar B, Zweig M, Cohen GH

Dept. Pathobiology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104

J Virol; 41(2):478-488 1982

We examined the properties of 17 monoclonal antibodies to glycoprotein gD of herpes simplex Type 1 (HSV-1) (gD-1) and HSV-2 (gD-2). The antibodies recognized eight separate determinants of gD, based on differences in radioimmuno-precipitation and neutralization assays. The determinants were distributed as follows: three were gD-1 specific, one was gD-2 specific, and four were type common. Several type-specific and type-common determinants appeared to be involved in neutralization. We developed a procedure for examining the effect that binding of monoclonal antibody has on proteolysis of native gD-1 by Staphylococcus aureus protease V8. We showed that several different patterns of protease V8 cleavage were obtained, depending on the monoclonal antibody used. The proteolysis patterns were generally consistent with the immunological groupings. With four groups of antibodies, we found that fragments of gD-1 remained bound to antibody after V8 treatment. A 38,000-dalton fragment remained bound to antibodies in three different groups of monoclonal antibodies. This fragment appeared to contain one type-common and two type-specific determinants. A 12,000-dalton fragment remained bound to antibodies belonging to one type-common group of monoclonal antibodies. Tryptic peptide analysis revealed that the 12,000-dalton fragment represented a portion of the 38,000-dalton fragment and was enriched in a type-common arginine tryptic peptide. (Author abstract) (29 Refs)

51. TYPING OF HERPES SIMPLEX VIRUS WITH TYPE-SPECIFIC HUMAN IMMUNOGLOBULIN M IN AN INDIRECT IMMUNOFLUORESCENCE ASSAY.

Spruance SL, Golden CA, Kern ER, Katz ME, Chow FS

Div. Infectious Diseases, Dept. Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132

J Clin Microbiol; 15(2):265-269 1982

Results of typing 29 herpes simplex viruses (HSV) isolated by an IgM indirect immunofluorescence assay and of finding individuals with type-specific IgM are reported. Determination of virus type was based on intensity of fluorescence of the substrate with HSV-1-and HSV-2-specific antisera after staining with fluorescein-conjugated anti-human IgM. Results were identical to those by restriction endonuclease digestion, and the assay appears to be accurate for the use in clinical virology laboratories. (11 Refs)

52. A RADIOIMMUNOASSAY FOR HERPES SIMPLEX VIRUS (HSV) THYMIDINE KINASE.

McGuirt PV, Keller PM, Elion GB

Dept. Experimental Therapy, Wellcome Res. Lab., Burroughs Wellcome Co., Res. Triangle Park, NC, 27709

Virology; 116(2):489-498 1982

A sensitive RIA for HSV-1 thymidine kinase (TK) has been developed. This assay is based on competition for the binding site of a rabbit antibody against purified HSV-1 TK, between a purified 3H-labeled HSV-1 TK and a sample containing an unknown amount of viral TK. The assay is capable of detecting 8 ng or more of the HSV enzyme. Purified HSV-1 TK denatured to less than 1% of its original kinase activity is as effective in binding to the antibody as is native HSV-1 TK. Viral TK is detectable at ranges of 150-460 ng/mg protein of cell extract from infected cells or cells transformed by HSV or HSV genetic material. HSV-2 TK appears highly cross-reactive, VZV TK is slightly less so, and the vaccinia TK shows little or no cross-reactivity. This RIA may serve as a tool for monitoring the expression of the HSV TK during an active herpes virus infection, a latent ganglionic infection, or in neoplastic cells which may have arisen by viral transformation. (Author abstract) (26 Refs)

53. EXPERIMENTAL ULCERATIVE HERPETIC KERATITIS. IV. PRELIMINARY OBSERVATIONS ON THE EFFICACY OF A HERPES SIMPLEX SUBUNIT VACCINE.

Carter CA, Hartley CE, Skinner GR, Turner SP, Easty DL

(c/o Easty), Bristol Eye Hosp., Lower Maudlin St., Bristol BS1 2LE, England

Br J Ophthalmol; 65(10):679-682 1981

Intramuscular administration of an inactivated type 1 herpes simplex virus (HSV) subunit vaccine in rabbits stimulated humoral and cellular immune responses and produced good levels of protection against corneal challenge with line HSV-1 virus. (22 Refs)

54. SELECTING BINDING AND COMPLEMENT-MEDIATED LYSIS OF HUMAN HEPATOMA CELLS (PLC/PRF/5) IN CULTURE BY MONOCLONAL ANTIBODIES TO HEPATITIS B SURFACE ANTIGEN.

Shouval D, Wands JR, Zurawski VR, Isselbacher KJ, Shafritz DA
(c/o Shafritz) Dept. Medicine and Cell Biology, Liver Res. Center, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 79(2):650-654 1982

High-affinity 125I-labeled monoclonal antibodies to hepatitis B virus surface antigen (HBsAg) bind to a human hepatocellular carcinoma cell line, PLC/PRF/5, which synthesizes and secretes HBsAg. These monoclonal antibodies of the IgG1, IgG2a, and IgM isotypes are directed against different antigenic determinants on HBsAg and, in the presence of complement, both anti-HBs IgG2a and IgM, but not anti-HBs IgG1, lyse PLC/PFR/5 cells in culture. Although there is a low level of anti-HBs binding (especially with anti-HBs IgM) to human hepatoma cell lines which do not synthesize HBsAg (SK-Hep 1 and Mahlavu cells), this interaction does not lead to complement-mediated cell lysis and is thought to be nonspecific. Minimal binding of 125I-labeled anti-influenza HA antigen IgM binding to PLC/PRF/5 cells was also detected, but this likewise did not lead to complement-mediated cell lysis. These results indicate that a human hepatocellular carcinoma cell line, persistently infected with hepatitis B virus, can be recognized and lysed by monoclonal antibodies directed against specific determinants of HBsAg. Monoclonal antibodies to this viral envelope protein may prove to be useful immunodiagnostic and immunotherapeutic agents when such viral epitopes are expressed on the surface of infected cells. (Author abstract) (33 Refs)

55. UNIFORM NOMENCLATURE FOR MONOCLONAL ANTIBODIES DIRECTED AGAINST VIRUS-CODED PROTEINS OF SIMIAN VIRUS 40 AND POLYOMA VIRUS.

Crawford L, Harlow E
Molecular Virology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
J Virol; 41(2):709 1982

A uniform nomenclature has been agreed upon for monoclonal antibodies directed against virus-coded proteins of simian virus 40 and polyoma virus. Blocks of numbers from PAb1 to PAb999 have been allocated to workers involved in the isolation of monoclonal antibodies of this type. The correspondence between PAb numbers and previously used names is given. (Author abstract) (6 Refs)

56. HUMAN ANTIBODIES RECOGNIZING THE ENVELOPE GLYCOPROTEIN OF THE BABOON ENDOGENOUS VIRUS (BAEV) ARE OF HETEROPHIL ORIGIN.

Wernicke D, Kurth R
(c/o Kurth), Paul-Ehrlich-Inst., Frankfurt, W. Germany
Med Microbiol Immunol (Berl); 170(2):135-143 1981

Human sera were tested for antibody reactions against purified envelope glycoprotein from baboon endogenous virus (BaEV). BaEV were produced by culturing in human rhabdomyosarcoma cells and dog thymus cells. Purified viral proteins were labeled with 125I. Sera were obtained from patients with leukemia, lymphoma, teratocarcinoma, or embryonal carcinoma and from normal healthy individuals. None of the sera reacted against the nonglycosylated major core protein p30 from BaEV. All sera reacted against the glycoprotein gp70 from BaEV grown in dog thymus cells (gp70dog) but not to gp70 from BaEV grown in human rhabdomyosarcoma cells. Tests using primarily sera from patients with teratocarcinoma showed that reactivity to gp70dog was blocked by soluble oligosaccharides or animal-cell lysates containing carbohydrates. When gp70dog was enzymatically deglycosylated, human sera no longer reacted. Results indicate that sera from normal individuals and patients with teratocarcinoma contain antibodies that recognize glycoproteins from the envelope of BaEV, and that these antibodies recognize the carbohydrate component of the glycoproteins. The carbohydrate component is apparently coded for by the genome of the host cell. (19 Refs)

57. ANTIBODIES AGAINST FELINE AND GIBBON APE REVERSE TRANSCRIPTASE ON SURFACE OF SPLEEN CELLS IN HUMAN MYELOGENOUS LEUKEMIA.

Jacquemin PC
Bruxels Branch, Ludwig Inst. Cancer Res., 74 Avenue Hippocrate, UCL 74.59, B-1200 Bruxelles, Belgique
Eur J Cancer Clin Oncol; 17(12):1283-1286 1981

We reported that antibody bound to blood leukocytes of patients in chronic myelogenous leukemia neutralize reverse transcriptase. The specificity of neutralization depended on the phase of the disease. Antibody bound to chronic phase leukemia cells neutralized Gibbon Ape leukemia virus reverse transcriptase, while that bound to blastic phase cells neutralized Feline leukemia virus reverse transcriptase. Spleen cells obtained from patients with chronic myelogenous leukemia have surface-bound immunoglobulins that recognize both reverse transcriptases. These data in the spleen suggest the existence of a progressive shift in cell population from a chronic phase type cell to a blastic phase type cell. (Author abstract) (9 Refs)

VIRAL STUDIES IN HUMAN CANCER

58. KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN.

Myskowski PL, Romano JF, Safai B
(c/o Safai) 425 E. 67th St., New York, NY, 10021
Cutis; 29(1):31-34 1982

The incidence, clinical features, associated conditions, pathogenesis, and prognosis of a new form of Kaposi's sarcoma (KS) are discussed. Within the last three yr 54 such cases showed differences from traditional KS including a mean age of 39 yr, all men with bisexual or homosexual preference, and geographic clustering in New York City and California. Clinical features of the new variant of KS include early presence of lymph node and/or mucous membrane involvement, pityriasis rosea-like pattern of skin lesions primarily on the head, trunk, and upper extremities, and systemic complaints. Associated conditions include pneumocystis carinii pneumonia, herpes simplex infection, toxoplasmosis, and cryptococcosis, but not secondary neoplasms. A history of prior sexually transmitted disease in new KS patients suggests a relationship to KS development. Cytomegalovirus infection was reported in 94% of cases. Immune defects are also suspected in young homosexual KS patients. The prognosis for the new form of KS is less favorable, with a 20% mortality rate at the present time. Effects of therapy are difficult to evaluate thus far. Awareness of the features of the new KS will enable practitioners to better recognize this disease. (18 Refs)

59. VULVAR INTRAEPITHELIAL NEOPLASIA: CORRELATION OF NUCLEAR DNA CONTENT AND THE PRESENCE OF A HUMAN PAPILLOMA VIRUS (HPV) STRUCTURAL ANTIGEN.

Crum CP, Braun LA, Shah KV, Fu YS, Levine RU, Fenoglio CM, Richart RM, Townsend DE

Div. Ob/Gyn Pathology, Columbia Univ. Coll. of Physicians and Surgeons, 630 West 168th St., New York, NY, 10032

Cancer; 49(3):468-471 1982

Immunoperoxidase localization of a human papilloma virus structural antigen (HPV) was attempted in 68 intraepithelial lesions of the vulva, 39 of which were analyzed for nuclear DNA content by microspectrophotometry. Overall, 5.9% (4/68) stained positive for HPV. Ninety per cent (35/39) of the cases tested were aneuploid, and, of these, 2.8% (1/35) stained positive for HPV. In contrast, 50% (2/4) of the polyploid lesions were positive. Hence DNA microspectrophotometry and immunoperoxidase localization of HPV are useful coparameters for distinguishing wart virus infection (condylomata) from vulvar intraepithelial neoplasia. HPV is detected infrequently within aneuploid lesions, in keeping with the concept that epithelial maturation is required for virion assembly. Whether the HPV genome exists in a nonreplicative state within the aneuploid cell population is unknown. (Author abstract) (18 Refs)

60. ANALYSIS OF HUMAN GENITAL WARTS (CONDYLOMATA ACUMINATA) AND OTHER GENITAL TUMORS FOR HUMAN PAPILLOMAVIRUS TYPE 6 DNA.

Gissmann L, De Villiers EM, Zur Hausen H

Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Strasse 11, 78 Freiburg, W. Germany

Int J Cancer; 29(2):143-146 1982

The 32-P-labeled cloned HPV 6 DNA was used as probe to analyze human genital tumors for DNA sequences homologous to HPV 6 DNA. Ninety three percent of all condylomata acuminata (41 out of 44) were found to harbor HPV 6 DNA. Of the remaining three, one contained HPV 1 DNA. No papillomavirus DNA was identified in the two other tumors. All three invasively growing giant condylomata acuminata (Buschke-Lowenstein tumors) investigated also contained HPV 6 DNA. Two out of six atypical condylomata of the cervix hybridized with HPV 6 DNA under stringent conditions, one only under conditions of low stringency. All DNA preparations from malignant tumors studied (54 cervical carcinomas, 10 penile carcinomas, 2 vulvar carcinomas) failed to anneal with HPV 6 DNA, even under conditions of low stringency. Although all HPV 6-positive condylomata acuminata analyzed in this study revealed HPV 6 DNA of regular mol wt (5.1 x 10(6)), two of the Buschke-Lowenstein tumors, as well as one of the two positive atypical condylomata of the cervix, contained HPV 6 DNA with a remarkable size heterogeneity. Apparently all size classes occurred in a supercoiled form without evidence for integration into host cell DNA. (Author abstract) (26 Refs)

61. HEPATOCELLULAR CARCINOMA ARISING IN NONCIRRHOTIC AND HIGHLY CIRRHOTIC LIVERS: A COMPARATIVE STUDY OF HISTOPATHOLOGY AND FREQUENCY OF HEPATITIS B MARKERS.

Okuda K, Nakashima T, Sakamoto K, Ikari T, Hidaka H, Kubo Y, Sakuma K, Motoike Y, Okuda H, Obata H

Dept. Medicine, Chiba Univ. Hosp., Chiba, Japan

Cancer; 49(3):450-455 1982

Hepatocellular carcinoma (HCC) associated with cirrhosis and HCC developing in a noncirrhotic liver may have differing pathogeneses. To study this possibility, 426 autopsied cases of HCC were investigated. Of these, 45 livers were not cirrhotic, 50 were highly cirrhotic (liver wt less than 99 g), and the remaining 331 were cirrhotic but not so highly. The av age was significantly older in the highly cirrhotic group, suggesting a longer premalignant period of chronic liver disease. The liver wt in the noncirrhotic group was about 3.5 times that in the highly cirrhotic group. Hepatitis B surface antigen was positive in serum in only 9.3% and in liver tissue in 10% in the noncirrhotic cases, the positivity rate being much lower compared with other groups (p less than 0.005-0.01), yet antibody to HB core was positive in 90%. The antibody titers were low, however, indicating that these noncirrhotic patients had in the past had HB virus (HBV) infection with no residual chronic B hepatitis. Analysis of the grades of anaplasia of cancer tissue demonstrated an inverse correlation between the degree of fibrosis and grade of anaplasia, i.e., the more advanced the fibrosis, the less anaplastic the cancer. These data suggest that HCC arising in highly cirrhotic livers and in noncirrhotic livers have different pathogenetic backgrounds, and that HBV infection, even though transient, has a certain role in hepatocarcinogenesis. The generally held conjecture that HCC in a noncirrhotic liver is caused by nonviral carcinogens and HCC arising on the ground of cirrhosis is due to HBV seems untenable in such a simple concept. (Author abstract) (27 Refs)

62. NATIONWIDE SURVEY OF MAJOR LIVER DISEASES IN THAILAND ANALYSIS OF 3,305 BIOPSIES AS TO YEAR-END 1978.

Bunyaratvej S, Meenakanit V, Tantachamrun T, Srinawat P, Susilaworn P, Chongchitnan N

Dept. Pathology, Faculty Medicine, Ramathibodi Hosp., Mahidol Univ., Bangkok 4, Thailand

J Med Assoc Thai; 64(9):432-439 1981

Liver cancer, cirrhoses, and inflammatory diseases were surveyed in different regions of Thailand. Liver cancer was more prevalent in the northeast (73.4% of all liver diseases) and in the north (Khonkaen) (42.5%) than in the south (36.8) and central (26.0%) areas. Hepatocellular carcinoma (HPC) was the most common liver cancer in the north (29.5), and cholangiocarcinoma (CC) was most frequently found in the northeast (46.2%). Metastatic carcinoma occurred more in the south (9.4%). HPC affected men 5x more than women, and men also were affected with CC twice as often as women. HPC rate reached a peak in the fifth decade and descended thereafter. Acute viral hepatitis comprised 2.1-4.3% of liver diseases in the different areas, chronic hepatitis 2.1-8.5%. While a high association between CC and opisthorchiasis has been reported, no significant association of viral hepatitis to opisthorchiasis associated CC could be found. Parasitic infections associated with the consumption of raw fish and high levels of nitrates and nitrites in food and surface waterss are discussed as factors in the regional patterns of liver disease. (29 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

63. EFFECT OF PROTEASE INHIBITORS ON THE ACTIVATION OF EPSTEIN-BARR VIRUS REPRESSED IN CULTURED LYMPHOID CELLS.

Morigaki T, Sugawara K, Ito Y
(c/o Ito) Dept. Micribiology, Faculty of Medicine, Kyoto Univ., Kyoto 606, Japan
Intervirology; 16(1):49-52 1981

The effects of five microbial and one synthetic protease inhibitor on the activation of Epstein-Barr virus expression in latently infected lymphoblastoid cells were studied. All protease inhibitors tested suppressed both viral antigen induction by 5-iododeoxyuridine treatment and cell growth in general. Among the inhibitors, however, antipain and pepstatin exerted a relatively strong and significant suppressive effect on antigen induction as compared to their inhibitory effect on cell growth. (Author abstract) (11 Refs)

64. INHIBITORY EFFECT OF RETINOIDS ON EPSTEIN-BARR VIRUS INDUCTION IN RAJI CELLS.

Zeng Y, Zhou HM, Zu SP
Inst. Virology, Chinese Academy Medical Sciences, Beijing, People's Republic of China
Intervirology; 16(1):29-32 1981

Induction of Epstein-Barr virus (EBV) early antigen after treatment with various combinations of croton oil and n-butyrate was markedely inhibited by retinoids 7901, 7902, Ro 10-9359 and Ro 11-1430. Possible administration of retinoids to virus capsid antigen IgA antibody-positive individuals in high-risk areas for nasopharyngeal carcinoma to prevent EBV activation and development of this cancer is discussed. (Author abstract) (12 Refs)

65. INCORPORATION OF E-5-(2-HALOVINYL)-2'-DEOXYURIDINES INTO DEOXYRIBONUCLEIC ACIDS OF HERPES SIMPLEX VIRUS TYPE 1-INFECTED CELLS.

Allaudeen HS, Chen MS, Lee JJ, De Clercq E, Prusoff WH
(c/o Prusoff) Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Biol Chem; 257(2):603-606 1982

E-5-(2-Bromovinyl)-2'-deoxyuridine (BrvdUrd) and E-5-(2-iodovinyl)-2'-deoxyuridine (IvdUrd) are among the most potent and selective inhibitors of herpes simplex virus type 1 (HSV-1) replication. To elucidate the site of inhibition, we examined whether the halovinyl analogs are incorporated into DNA using two approaches: (i) In assays with purified DNA polymerases omitting dTTP from the reaction system, addition of either BrvdUTP or IvdUTP increased the polymerization reaction, indicating that these two analog triphosphates can be alternate substrates. (ii) When HSV-1-infected Vero cells were grown in the presence of either BrvdUrd or IvdUrd, there was an increase in the density of both the viral and cellular DNA. The viral DNA had 40% of its thymidine moiety substituted by IvdUrd when the concentration of [125I]IvdUrd was 24 uM (in the absence of added thymidine). At 30 uM BrvdUrd and 1 uM [2-14C]thymidine, the viral DNA had only 11% of its thymidine moiety substituted by BrvdUrd, presumably because of the presence of added thymidine. Following digestion of [125I]IvdUrd-substituted DNA with DNase 1, venom phosphodiesterase, and alkaline phosphatase, the radioactivity co-migrated with nonradioactive IvdUrd in thin layer chromatography. Under similar conditions, no detectable incorporation of either [125I]IvdUrd or BrvdUrd into mock-infected Vero cell DNA was observed. Thus, IvdUrd and BrvdUrd are incorporated into DNA of HSV-1 infected cells but not into DNA of uninfected cells. (Author abstract) (22 Refs)

66. STUDIES ON BENZHYDRAZONE, A SPECIFIC INHIBITOR OF HERPESVIRUS GLYCOPROTEIN SYNTHESIS. SIZE DISTRIBUTION OF GLYCOPEPTIDES AND ENDO-BETA-N-ACETYLGLUCOSAMINIDASE-H TREATMENT.

Serafini-Cessi F, Campadelli-Fiume G
Istituto di Patologia Generale, Universita di Bologna, Bologna, Italy
Arch Virol; 70(4):331-343 1981

Benzhydrazone is a bis-amidinohydrazone derivative which specifically hinders the formation of herpes simplex virus (HSV) glycoproteins. In this study we present some structural features of the oligosaccharide chains of herpesvirus glycoproteins synthesized in cells incubated with the inhibitor. Gel filtration analysis of glycopeptides, obtained through exhaustive pronase-digestion of infected cells after a long or a short labelling with 14C-glucosamine, showed that benzhydrazone reduced the appearance of glycopeptides of all the size-classes, including the mannose-rich glycopeptide with an approximate molecular weight of 1,500. The same per cent of label was released from both untreated and benzhydrazone-treated cells after digestion with endo-beta-N-acetylglucosaminidase H, an enzyme which cleaves between the N-acetylglucosamine residues in large high-mannose type oligosaccharides. This indicates that the relative amount of glycoproteins sensitive to this enzyme did not differ in the two kinds of samples. PAGE analysis confirmed that the same glycoproteins were digested in both samples. They were gA, pgC, and pgD, which therefore contain high-mannose type oligosaccharides. It is concluded that benzhydrazone hinders carbohydrate addition to herpesvirus proteins at an early step. (Author abstract) (34 Refs)

67. INTERFERONS AND INTERFERON INDUCERS: DEVELOPMENT OF CLINICAL USEFULNESS AND THERAPEUTIC PROMISE.

Pollard RB
Dept. Internal Medicine, Div. Infectious Diseases, Univ. Texas Medical Branch, 5-17 McCullough, Galveston, TX, 77550
Drugs; 23(1/2):37-55 1982

Studies concerning applications of interferon (IF) and IF-inducers in humans are discussed. General properties, pharmacokinetics, indications for use, and adverse reactions of IF are reviewed. Therapeutic trials discussed include measurement of efficacy, local and systemic administration of IF focusing on systemic administration against herpesviruses, hepatitis B virus infections, and antitumor applications. Therapeutic trials with various IF-inducers are discussed: viral inducers, pyran copolymer and tilorone, and polyinosinic-polycytidylic acid. (127 Refs)

68. SPECIES SPECIFICITY OF INTERFERON ACTION: A FUNCTIONING HOMOSPECIFIC NUCLEUS IS REQUIRED FOR INDUCTION OF ANTIVIRAL ACTIVITY IN HETEROKARYONS.

Sakaguchi AY, Stevenson D, Gordon I
(c/o Gordon) Dept. Microbiology, Sch. Medicine, Univ. Southern California, Los Angeles, CA, 90033
Virology; 116(2):441-453 1982

We have investigated whether a homospecific nucleus might be necessary in order for a species-specific interferon (IFN) to protect heterokaryons and cybrids against viral infection. We used mouse fibroblast interferon (Mu-IFN-beta) and human leukocyte interferon (Hu-IFN-alpha) to induce resistance to vesicular stomatitis virus (VSV) replication in single cells, polykaryons, or cybrids. When we fused intact mouse L-929 fibroblasts to intact human HEL fibroblasts with polyethylene glycol (PEG), we found that the single mouse cells and mouse homopolykaryons were protected only by the mouse IFN; that the single human cells and human homopolykaryons were protected only by the human IFN; and that the heteropolykaryons were protected by both IFNs. When we constructed the mouse-human heterokaryons from L-929 cells whose DNA has been crosslinked by treatment with Trioxsalen and near UV light (320-360 nm), however, they were protected only by the human IFN, not by the mouse IFN. We also continuously exposed mouse cells with intact nuclei to cycloheximide (CH) throughout their fusion with PEG, their subsequent brief treatment with IFN, and the termination of the IFN 'pulse' with anti-IFN antibody. The CH was then removed, allowing protein synthesis to resume. The fused mouse cells nevertheless resisted VSV infection. This result suggests that the lack of response to mouse IFN of the human-mouse heterokaryons with inactivated mouse nuclei, and of the cybrids, was not due to PEG-induced loss or dysfunction of species-specific IFN receptors in cells incapable of resynthesizing them. Our data support the hypothesis that a homospecific nucleus is needed in order for some species-specific IFNs to protect cells against viral infection and hence that the nucleus is involved in a selective response to IFN. (34 Refs)

69. MECHANISM OF INTERFERON ACTIVITY. STABILITY AND TRANSLATION OF SIMIAN VIRUS-40 EARLY MRNA CODING FOR T-ANTIGEN IS COMPARABLE IN UNTREATED AND INTERFERON-TREATED MONKEY CELLS.

Daher KA, Samuel CE
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
Biochem Biophys Res Commun; 101(2):697-703 1981

Effects of interferon (IF)-treatment on the translation and functional stability of Simian virus 40 (SV40) early messenger (m)RNA coding for T-antigen under conditions where SV40 early RNA synthesis is apparently unaffected by IF were investigated. African green monkey kidney cells were infected with a tsA mutant of SV40 at an elevated temperature (40 C). The rate of T-antigen synthesis in tsA-infected cells at varying times following the addition of 1 ug/ml actinomycin D to the medium 36 hr post infection was determined to decide whether the stability of SV40 early mRNA differed between untreated and IF-treated cells. The SV40 mRNA coding for T-antigen had a half-life of about 3 hr, and there was no significant difference between the IF-treated and untreated cells. The fact that the decay of SV40 early RNA is indistinguishable between the IF-treated and untreated cells was thought to augment other facts and indicate that an enhanced degradation of SV40 early RNA by an IF-mediated RNAase probably does not play a major role in the antiviral action of IF in SV40 lytic infections. (25 Refs)

GENERAL REVIEWS

70. HERPES SIMPLEX.

Fanta D
Rooseveltstrasse 12/5, A-4400 Steyr, Austria
Wien Klin Wochenschr; 93(24):739-744 1981

Differentiation, contagiousness, localization, recurrences, immunology, diagnosis, therapy, and oncogenic potential of Herpesvirus hominis (HSV) Type 1 and Type 2 are reviewed and recent findings are presented. Observations indicate that HSV and other herpesviruses are potential oncogenic agents. Female patients with recurrent genital HSV infections should be classified as risk patients and have regular check-up. (34 Refs) (In GER)

71. NONGONOCOCCAL URETHRITIS AND OTHER SELECTED SEXUALLY TRANSMITTED DISEASES OF PUBLIC HEALTH IMPORTANCE.

WHO Scientific Group, Albritton W, Belli L, Black F, Bowie W, Catterall RD, Corey L, Delektorskij VV, Dunkelberg WE, Holmes KK, Lang DJ, Mardh PA, Muller M, Oriel JD, Osoba AO, Pasmanik I, Schachter J, Siboulet A, Sing EH, Sowmini CN, Taylor-Robinson D, Westrom L, Wiesner PJ, Antal GM, Causse Y
Geneva, Switzerland
WHO Tech Rep Ser (660): 142 pp., 1981.

Sexually transmitted diseases with focus on infections caused by Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Haemophilus ducreyi, and infections with genital herpes simplex virus, cytomegaloviruses and other agents are discussed. Epidemiology, pathogenesis, diagnosis, prevention,and treatment of the infections are presented. Vulvovaginitis, cervicitis, and urethritis in women, genital ulcers, epididymitis, and management of the diseases are reviewed. (195 Refs)

72. CONDYLOMATA ACUMINATA.

Luger A, Gschnait F
Dermatologische Abteilung, Krankenhaus der Stadt Wien-Lainz, Wolkersbergenstrasse 1, A-1130 Wien, Austria
Wien Klin Wochenschr, 93(24):746-750 1981

Definition, immunology, infection, epidemiology, clinical manifestation, histology of condylomata acuminata (CA), surgical treatment, and topic treatment with cytostatic substances, cryotherapy, and liquid nitrogen are discussed. Human papilloma virus causes CA which are infectious and transferable by direct contact. Greatly proliferating CA may lead to malignant degeneration. (35 Refs) (In GER)

73. REGULATION OF SV40 GENE EXPRESSION.

Graessmann A, Graessmann M, Mueller C
Institut fur Molekularbiologie und Biochemie, Freien Universitat Berlin, Berlin, W. Germany
Adv Cancer Res; 35:111-149 1981

The microinjection approach to the study of simian virus 40 (SV40) and polyoma virus (PV) gene expression is discussed. The technique permits placing of biological material from virtually any source directly into living, single-tissue culture cells using glass micropipettes. Cell type dependence of SV40 and PV gene expression is presented in relation to permissive, non-permissive, semi-permissive, and virus-resistant cells. Functions of SV40 tumor antigens are considered, including induction of cellular and viral DNA systems, regulation of late and early SV40 gene expression, stimulation of rRNA synthesis, helper function for adenovirus and U antigenicity, and reduction of the actin cable structure. Experiments with microinjection of SV40 DNA fragments to induce cellular transformation and applications of microinjection are reviewed. (78 Refs)

OTHER RELATED STUDIES

74. SERIOUS INFECTIONS DURING CONTINUING TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA.

Ninane J, Chessells JM
Dept. Hematology, Hosp. for Sick Children, Gt Ormond St., London WC1N 3JH, England
Arch Dis Child; 56(11):841-844 1981

Seventy-six of 168 children with acute lymphoblastic leukemia, who had completed induction therapy and central nervous system prophylaxis, were each admitted to hospital at least once during subsequent treatment with an infectious illness. The time spent in hospital was calculated as a proportion of the total number of days at risk and had a mean value of one day in 75. Sixty-three (37%) children spent longer than this in hospital, particularly patients younger than 5 years and those on a more intensive protocol; a 3rd year of treatment appeared to carry no significant additional risk of infection. Death due to infection occurred in 14 (8.3%) children; these deaths were more common in younger patients and during the first 2 years of treatment and were mainly due to measles, septicemia, or cytomegalovirus. These findings show that younger children and those receiving more intensive treatment are at greater risk of infection. The risk is not one of exotic infections, but of measles, a preventable disease. (Author abstract) (15 Refs)

75. INDUCTION OF HOST DNA SYNTHESIS BY HUMAN CYTOMEGALOVIRUS IN SENESCENT HUMAN DIPLOID CELLS (MEETING ABSTRACT).

Tsuji Y, Ide T, Mitsui Y, Toba M, Ishibashi S
Hiroshima University School of Medicine, Hiroshima, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Human diploid cells have limited life span (in vitro senescence). Tumor viruses induce host DNA synthesis in quiescent young cells, but transformed human cells sometimes cease to grow after various periods of their intrinsic life span. Do tumor viruses have ability to induce proliferation of senescent human diploid cells? TIG-1, human diploid cells, cease to grow at about 60-62 PDL. Fresh medium containing 10% fetal calf serum (FCS) or replating induce DNA synthesis in less than 0.1% of these cells. Infection with human cytomegalovirus (moi 1-10) seemed to bring about host DNA synthesis as judged from the following results: 1) Incorporation of 3H-thymidine into DNA increased up to 10-fold. 2) Percentage of labeled nuclei raised more than 50 x. 3) CsCl centrifugation of DNA showed that host DNA synthesis occurred 2 days after infection and thereafter viral DNA synthesis took place. 4) CsCl centrifugation of DNA labeled with 5-bromo-2'deoxyuridine (BUdR) proved replication of DNA rather than repair synthesis. 4) Polyamine contents in infected cells increased up to 10 x, whereas not in cells cultured in 10% FCS. (no Refs)

76. HEPATITIS B VIRUS INFECTION IN MEDICAL AND HEALTH CARE PERSONNEL.

Callender ME, White Y, Williams R
(c/o Williams) Liver Unit, King's Coll. Hosp. and Medical Sch., London SE5 8RX, England
Br Med J; 284(6312):324-326 1982

An analysis of 51 cases of hepatitis B virus infection in health care workers admitted as patients to the liver unit over 7 yr showed 3 healthy carriers of hepatitis B virus, 7 cases of fulminant hepatic failure, 13 cases of acute hepatitis, 6 cases of chronic persistent hepatitis, 17 cases of c hronic active hepatitis (of whom 11 had cirrhosis), and 5 cases of hepatocellular carcinoma. To date 11 of these patients have died. Only 15 of the 51 patients had a history of direct occupational exposure and only 3 patients could recall specific inoculation injuries. In contrast, the source of infection was apparent in 32 of 50 consecutive cases of fulminant hepatic failure or acute hepatitis B in non-medical staff. Since specific inoculation injuries are not the usual mode of infection in medical staff and since only a few of the patients who are hepatitis B virus carriers will be detected by selective screening of 'high-risk' patients, the overall risk of infection can be reduced only by stricter precautions in the handling of any patient's blood and by the use of hepatitis B virus vaccines for medical staff at high risk. (Author abstract) (27 Refs)

77. IMMUNIZATION AGAINST INFLUENZA IN CHILDREN WITH CANCER: RESULTS OF A THREE-DOSE TRIAL.

Brown AE, Steinherz PG, Miller DR, Armstrong D, Kellick MG, Gross PA, Davis AE
Memorial Sloan-Kettering Cancer Center, New York, NY
J Infect Dis; 145(1):126 1982

Immunization against influenza is recommended for children with neoplastic diseases despite poor immunogenicity in those receiving concomitant chemotherapy. The data show that a third dose of trivalent influenza virus vaccine does not significantly increase the number of children receiving chemotherapy who achieve HAI antibody titers of greater than or equal to 1:32 regardless of the vaccine antigen. Children with cancer who were not receiving chemotherapy achieved HAI antibody titers of greater than or equal to 1:32 with the same frequency as did normal children in the national study. These results confirm previous studies that show that primary immunization with influenza virus vaccine often is not immunogenic in children with neoplastic diseases who are receiving concomitant chemotherapy. The 'recall of the old antigen' (A/Texas/1/77 [H3N2]) is less hampered by the chemotherapy status. Other methods of immunization, such as adjusted schedules of immunization and, possibly, adjuvants and immunopotentiators, should be examined to determine how to immunize cancer patients successfully against newer strains of influenza virus. (Author abstract) (3 Refs)

78. PERSISTENCE OF ANTIBODY AFTER THE ADMINISTRATION OF INFLUENZA VACCINE TO CHILDREN WITH CANCER.

Sumaya CV, Williams TE
Dept. Pediatrics, Univ. Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX, 78284
Pediatrics; 69(2):226-229 1982

Children with cancer who received an intramuscular injection of inactivated split or whole bivalent (A/New Jersey/76-A/Victoria/75) influenza virus vaccine during the fall of 1976 were tested up to 18 mo later for the persistence of antibody. Titers of antibody greater than or equal to 10 to influenza A/New Jersey/76 virus were present in the sera of 34 children 2 wk after immunization. The geometric mean titer was 40.0. Eighteen mo later a titer greater than or equal to 10 was present in 13 (38%) children; the geometric mean titer was 8.5. Of 36 children with a titer of antibody greater than or equal to 10 to A/Victoria/75 virus 2 wk after immunization, 34 still had a detectable titer in the later examination. The geometric mean titer declined from 65.3 to 25.6. Titers of antibody to B/Hong Kong/72 virus (not included in the vaccine) remained relatively stable. In 11 children the usual chemotherapy was discontinued during the study. The shorter persistence of antibody to A/New Jersey/76 virus, in contrast to that of the other two influenza viruses tested, was associated with a lack of prior exposure to the virus and the absence of subsequent natural infection with this virus or an antigenically related subtype. The potential effect of cancer chemotherapy on the persistence of antibody levels is unclear. (Author abstract) (18 Refs)

79. SPECIFIC IMMUNOTHERAPY WITH VACCINIA ONCOLYSATES.

Wallack MK
Dept. Surgery, Washington Univ. Sch. Medicine, 4960 Audubon Ave., St. Louis, MO, 63110
Cancer Immunol Immunother; 12(1):1-4 1981

A preliminary trial of live vaccinia virus-augmented lysed tumor cell vaccine (vaccinia oncolysate) was conducted; 29 patients with overwhelming metastasis after resection of primary tumor were given a dose of 5 x 10(6) vaccinia oncolysate/ml every wk for 6 mo and every 2 wk for 18 mo or until progression. The treatment was tolerated well, but 20 patients died during the trial. Nine patients seemed to develop stable disease; all of them had repeated delayed hypersensitivity responses to the vaccine, as did about half of the patients who did not survive. (10 Refs)

80. SYNTHESIS AND STABILITIES OF PROTEINS RELATED TO THE POLYOMA SMALL T ANTIGEN IN ESCHERICHIA COLI.

Horwich A, Koop AH, Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Mol Cell Biol; 2(1):88-92 1982

Early proteins (T antigens) encoded by polyoma and simian virus 40 which are involved in virus replication and neoplastic cell transformation were found to also be synthesized in Escherichia coli. A protein with N terminus derived from polyoma was significantly more unstable than a similar protein with N terminus derived from beta-galactosaminidase. (6 Refs)

81. INTERFERON: IMMUNOBIOLOGY AND CLINICAL SIGNIFICANCE.

Stiehm ER, Kronenberg LH, Rosenblatt HM, Bryson Y, Merigan TC
Dept. Pediatrics, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Ann Intern Med; 96(1):80-93 1982

Interferons are proteins elaborated by infected cells that protect noninfected cells from viral infection. These proteins produce a temporary 'antiviral state' by altering nucleotide metabolism and cytoplasmic enzyme induction. Interferons appear early after viral infection locally and systematically to limit spread of viral infection; they also affect cell differentiation, growth, surface antigen expression, morphologic findings, and immunoregulation. Several human disorders have diminished interferon production. Newborns have normal interferon alpha but deficient interferon gamma production. Infants with congenital infections may also have defects in interferon production. Immunosuppressed patients receiving transplants (marrow, heart, or kidney) have diminished interferon production, particularly immediately after transplant. Deficiencies of interferon have also been noted in Down's syndrome, cellular immunodeficiencies, uremia, malnutrition, and hematopoietic malignancy. Leukocyte interferon has been of therapeutic value in herpes zoster infections, in patients with cancer, and in patients with hepatitis B infection. Interferon has not been proved to help children with congenital cytomegalovirus or rubella. Interferon can shrink lymphoid tumors, particularly non-Hodgkin's lymphoma. (Author abstract) (160 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. PURIFICATION OF GLYCOPROTEIN GD OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 BY USE OF MONOCLONAL ANTIBODY.

Eisenberg RJ, Ponce de Leon M, Pereira L, Long D, Cohen GH
Dept. Pathobiology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Virol; 41(3):1099-1104 1982

Glycoproteins gD-1 and gD-2 of herpes simplex virus Types 1 and 2, respectively, were purified on an immunoadsorbent consisting of the type-common monoclonal antibody HD-1 linked to Sepharose. Each glycoprotein was of sufficient purity, quantity, and biological activity to be used for immunological and biochemical studies. Each glycoprotein induced high titers of type-common monospecific neutralizing antibody in mice. Amino acid analysis indicated that gD-1 and gD-2 had similar though not identical amino acid compositions. (Author abstract) (22 Refs)

2. INCIDENCE OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 ISOLATED IN PATIENTS WITH HERPES GENITALIS IN SHEFFIELD.

Barton IG, Kinghorn GR, Najem S, Al-Omar LS, Potter CW
Dept. Virology, Univ Sheffield Medical Sch., Beech Hill Road, Sheffield S10 2RX, England
Br J Vener Dis; 58(1):44-47 1982

The incidence of herpes simplex virus (HSV)-1 and HSV-2 in genital lesions from 31 patients presenting with clinical features of herpes genitalis was determined by polypeptide analysis of virus proteins in sodium dodecyl sulfate polyacrylamide gels. The principal feature used to identify the strain of virus was the mol wt of the major capsid protein which is greater in HSV-2 than HSV-1. All the strains of HSV-1 analyzed gave rise to a heavily labeled band of mol wt 122,000 which was absent from all the strains of HSV-2 examined. Twenty-five isolates were also typed by the restriction enzyme technic. In all 25 isolates, the polypeptide and restriction endonuclease analyses were in agreement. Of the 31 isolates, 19 were HSV-1. No apparent correlation was observed between virus and the nature of the genital lesion; however, most of the isolates from men with primary infections were Type I. There was no marked difference between the incidence of HSV-1 in primary (14/22) and recurrent (5/9) infections. (19 Refs)

3. FACTORS AFFECTING RECOVERY OF LATENT HERPES SIMPLEX VIRUS FROM HUMAN TRIGEMINAL GANGLIA.

Lewis ME, Warren KG, Jeffrey VM, Shnitka TK
Dept. Medicine, Univ. Alberta, Edmonton, Alberta T6G 2G3, Canada
Can J Microbiol; 28(1):123-129 1982

The rate of recovery of herpes simplex virus (HSV) from human trigeminal ganglia explant monolayers is affected by two factors: (1) time elapsed from the death of an individual to the establishment of in vitro culture of ganglia and (2) surface area onto which ganglia are explanted. Spontaneous reactivation of HSV from human trigeminal ganglia can be maximized when ganglia are obtained within 12 hr of death and explanted onto a surface area of 250 cm2. Viruses isolated by explantation of human trigeminal ganglia were found to be uniformly HSV Type 1 by restriction enzyme analysis. (Author abstract) (18 Refs)

4. CHARACTERIZATION OF HEAVY PARTICLES OF ADENO-ASSOCIATED VIRUS TYPE 1.

Lipps BV, Mayor HD
(c/o Mayor) Dept. Microbiology and Immunology, Baylor Coll. Medicine, Houston, TX, 77030
J Gen Virol; 58(part1):63-72 1982

The temperature-sensitive mutant ts4 of adenovirus type 2 (Ad-2) is capable of c omplementing adeno-associated virus type 1 (AAV-1) in HEp2, KB and HEK cells at 34 C and 39 C when used as a helper virus. Heavy non-infectious AAV-1 particles can be generated by using the mutant ts4 in HEp2 cells. When AAV-1 is grown in serial passages in HEp2 cells, both the wild-type Ad-2 and the mutant ts4 give rise to heavy, less infectious AAV-1 particles. The heavy AAV-1 particles generated by Ad-2 in advanced serial passages retain the property of having CF and IF antigens, but the AAV-1 generated by the mutant in advanced serial passages lose this property. There is no appreciable difference in the particle counts made by electron microscopy of AAV-1 preparations generated either by Ad-2 or the mutant ts4. Analysis by polyacrylamide gel electrophoresis of purified heavy AAV generated by ts4 indicates that in late passage an additional polypeptide of higher mol wt than the three structural polypeptides is detected. (Author abstract) (37 Refs)

5. CIS AND TRANS-DIAMMINEDICHLOROPLATINUM(II) BINDING PRODUCES DIFFERENT TERTIARY STRUCTURAL CHANGES ON SV40 DNA.

Scovell WM, Kroos LR
Dept. Chemistry, Bowling Green State Univ., Bowling Green, OH, 43403
Biochem Biophys Res Commun; 104(4):1597-1603 1982

Tertiary structural changes produced by cis-diamminedichloroplatinum(II) (cisDDP) and trans-diamminedichloroplatinum(II) (trans-DDP) binding on simian virus 40 (SV40) DNA was studied by gel electrophoresis, assuming that the mobility of the DNA is proportional to the absolute number of supercoils. The Pt bound to DNA was determined by atomic absorption spectrophotometry after unbound Pt was separated by drop dialysis. Cis-DDP binding unwinds the supercoiled DNA to the intact relaxed form in about 6 hr, which is about 4x faster than observed for trans-DDP. When the SV40 DNA is incubated with the isomers for up to 30 min, cis-DDP reduces the mobility of supercoiled DNA at very short reaction times, an effect produced with trans-DDP only after an interval 50x longer. Results suggest that the cis-isomer exhibits a mode of binding different than that of the trans-isomer, a mode which is responsible for the more effective unwinding of the DNA. (29 Refs)

6. NEW HUMAN PAPOVAVIRIDAE VIRUSES.

Shevliagin VIa
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Usp Sovrem Biol; 92(3):338-353 1981

Isolation, physico-chemical, antigenic, and biological properties of new viruses from Papovaviridae family are reviewed. In addition to simian virus SV-40, Papovaviridae group includes BK virus isolated from the urine of a patient subjected to kidney transplantation, and JCV virus isolated from a patient with Hodgkin's disease complicated by progressive multifocal encephalopathy. BK virus was shown to induce sarcomas, ependymomas and insulinomas in Syrian hamsters; the incidence and latent period depended upon the route of administration and the degree of virus purification. BK virus failed to induce tumors in rabbits, guinea pigs, young rats, and monkeys. JCV virus showed replication only in the glial cells of human embryo. The intracranial or sc inoculation with JCV virus produced malignant gliomas and pineocytomas in Syrian hamsters. Peripheral neuroblastomas with metastases to the liver, bone marrow, and lymph nodes were observed after intraocular infection with JCV virus. (140 Refs) (In RUS)

7. PRIMARY STRUCTURE ANALYSIS OF THE MAJOR INTERNAL PROTEIN P24 OF HUMAN TYPE C T-CELL LEUKEMIA VIRUS.

Oroszlan S, Sarngadharan MG, Copeland TD, Kalyanaraman VS, Gilden RV, Gallo RC
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 79(4,part1):1291-1294 1982

A human type C retrovirus [human T-cell leukemia (lymphoma) virus; HTLV], recently isolated from young adult patients with cutaneous T-cell lymphoma or leukemia, was not detectably related to other known animal retroviruses in molecular hybridization studies, by comparison of reverse transcriptase and the major core protein p24. The p24 core protein was purified to homogeneity. The amino acid composition, the COOH-terminal amino acid, and the NH2-terminal amino acid sequence of the first 25 residues of this major internal structural protein were determined. These results were then compared to the known structure of the internal core protein of other retroviruses. The compositional data reveal that HTLV p24 is chemically distinct from p30-p24 of other animal retroviruses, in agreement with the earlier immunological analyses. However, HTLV p24 shares the common NH2-terminal proline and COOH-terminal leucine of all mammalian type C viral p30s. In addition, like bovine leukemia virus (BLV), HTLV lacks the common prolylleucylarginine tripeptide and the larger conserved region found near the NH2 terminus of the other mammalian type C viral p30s. Alignment of the amino acid sequence of HTLV p24 with previously determined sequences of other retrovirus proteins, including BLV p24, reveals statistically significant sequence homology only to BLV. The results reported here demonstrate that HTLV p24 is related to but chemically distinct from the major core protein of other retroviruses. Similarly, previous results showed that there was no immunological crossreactivity of the p24 protein and reverse transcriptase of HTLV with other retroviruses, including BLV, and no nucleic acid sequence homology. However, the present results, combined with the common size of the p24 and reverse transcriptase, suggest that HTLV may be closer to BLV than any other known retrovirus. (Author abstract) (23 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

8. CELL SURFACE GLYCOPROTEIN PATTERNS OF TWO EBV-NEGATIVE LINES AND THEIR EBV CONVERTED SUBLINES.

Koide N, Wells A, Klein G, Ernberg I
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Intervirology; 16(3):142-148 1981

Cell surface galactosyl-glycoprotein patterns were compared between Ramos and BJAB, two Epstein-Barr virus (EBV)-negative Burkitt lymphoma lines, and their acutely EBV-superinfected and stably EBV-converted derivatives. A major difference between Ramos and its EBV-infected variants was the appearance of a 69,000 mol wt galactosyl-glycoprotein (GP 69) in the latter. The same phenomenon was found in BJAB along with the additional appearance of a 71,000 mol wt galactosylglycoprotein (GP71) in the EBV-infected cells. GP71 was present in Ramos and in its EBV-converted derivatives. (Author abstract) (23 Refs)

9. ANTIVIRAL SPECIFICITIES OF IMMUNOGLOBULINS SECRETED BY HUMAN LYMPHOCYTES IMMORTALIZED IN VITRO WITH EPSTEIN-BARR VIRUS.

Seigneurin JM, Desgranges C, Reneversez JC, Baccard M, Micouin C
Laboratoire de Virologie, Centre Hospitalier Universitaire, Grenoble, France
Ann Virol; 132(3):323-335 1981

Human B lymphocytes from a chronic T-lymphocytic leukemia patient were immortalized through the use of two Epstein-Barr (EBV) strains, both obtained after passage in marmoset lymphocytes, Ma-B95-8 from an infectious mononucleosis patient, and Ma-M81 from lymphocytes invading the tumor of a nasopharyngeal carcinoma patient. Features of the two established cell lines are described especially in relation to polyclonal synthesis of virus specific antibodies. Characteristics of the patient's lymphocytes are described. The two cell lines established were clearly of B-cell origin. Both cell lines contained Epstein-Barr nuclear antigen in 100% of the cells. EBV early antigen was evident in 1.8% of Ma-B95 cells and 3.0% of Ma-M81 cells. EBV viral capsid antigen was found only in 3.0% of Ma-M81 cells. Both lines expressed complement 3 and EBV receptors and surface-bound immunoglobulin. Ultrastructurally, Ma-M81 had the typical features of a lymphoblastoid cell line, while Ma-B95 had features of plasmacytoid cells. Ma-B95 cells secreted a high level of immunoglobulins (32 ug/10(6) cells), including 24 ug IgG, while Ma-M81 cells produced only 3.8 ug. At the time the cell lines were established, the patient possessed antiviral antibodies against several viruses, cytomegalovirus, respiratory syncytial virus, and measles virus, which were found in the immunoglobulin secreted by Ma-B95. The Ma-M81 cell line produced complete EBV virion, while in the Ma-B95 cells the replicative cycle of EBV was blocked at the early antigen stage. (39 Refs)

10. DNA-POLYMERASE INDUCED BY HERPESVIRUS PAPIO (HVP) IN CELLS OF LYMPHOBLASTOID CULTURES DERIVED FROM LYMPHOMATOUS BABOONS. - REPORT V.

Djachenko AG, Lapin BA
(c/o Lapin) Inst. Experimental Pathology and Therapy, USSR Acad. Medical Science s, Gora Trapetziya, P. B. 66, Sukhumi, USSR
Exp Pathol; 20(1):51-57 1981

A new DNA-polymerase was found in the cells of suspension lymphoblastoid cultures which produce lymphotropic baboon herpesvirus (HVP). This enzyme was isolated in a partially purified form. Some of its properties vary from those of other cellular DNA-polymerases. HVP-induced DNA-polymerase has a molecular weight of 160,000 and sedimentation coefficent of about 8 S. The enzyme is resistant to high salt concentration and N-ethylmaleimide, but it is very sensitive to phosphonoacetate. It effectively copies 'activated' DNA and synthetic deoxyribohomopolymers. Attempts to reveal the

DNA-polymerase activity in HVP virions were unsuccessful. (Author abstract) (15 Refs)

11. CORRELATION BETWEEN HUMAN PAPILLOMAVIRUS (HPV) TYPE AND HISTOLOGY OF WARTS.

Gross G, Pfister H, Hagedorn M, Gissmann L

Universitats-Hautklinik Freiburg, Hauptstrasse 7, 7800 Freiburg i Br., W. Germany

J Invest Dermatol; 78(2):160-164 1982

Forty warts from different patients and of different clinical type were examined histologically and virologically. Eight lesions were found to be associated with human papillomavirus Type 1 (HPV 1), 15 tumors were induced by HPV 2, HPV 3 was detected 4 times, HPV 4 twice, and HPV 6 11 times. HPV3, HPV 4, and HPV 6 induced warts revealed a correlation between histology and virus type. They are characterized by the so called 'edematous type clear cells'. In HPV 3 associated flat warts pycnotic nuclei were mainly localized in the center of large vacuoles. In genital warts sickle shaped nuclei were pushed to the margin of the vacuolized cells. The histology of HPV 1 and HPV 2 induced warts was more heterogenous. With one exception HPV 1-induced lesions represented typical myrmecia warts, varying in the number and shape of inclusion bodies. HPV 2 associated common warts, however, revealed three very distinct histologic features: (1) inclusion wart typical for HPV 1; (2) classical common wart with marked condensation of keratohyalin granules; (3) warts with extreme vacuolization of squamous and granular cells leading to a honeycomb-like picture. (Author abstract) (25 Refs)

VIRUS REPLICATION AND EXPRESSION

12. EFFECTS OF N-BUTYRATE ON EPSTEIN-BARR VIRUS-CARRYING LYMPHOMA LINES.

Anisimova E, Saemundsen AK, Roubal J, Vonka V, Klein G

(c/o Saemundsen) Dept. Tumor Biology, Karolinska Institutet, S104 01 Stockholm, Sweden

J Gen Virol; 58(part1):163-171 1982

The compound n-butyrate has been shown to induce Epstein-Barr virus (EBV) antigen synthesis in certain EBV-carrying lymphoma lines. We have studied the effect of n-butyrate on two EBV-positive Burkitt lymphoma lines by immunofluorescence and electron microscopy. In the producer line P3HR-1, the drug induced not only early antigen (EA) and virus capsid antigen (VCA) synthesis, as shown before, but also increased the number of cells containing virus particles. The transition from VCA expression to the formation of virus particles was much more effective in treated cells than in EBV antigen-producing cells of the same line. The productive cycle was associated with the development of characteristic morphological changes. In the non-producer Raji cells, n-butyrate induced EA in only a minor fraction of the cells. There were, however, clear signs of differentiation in the direction of plasma cells. Two days after the addition of n-butyrate 80% of the Raji cells could be classified as plasmablasts. After 72 hr, 20% of the cells appeared as typical plasma cells. (Author abstract) (33 Refs)

13. THE ACTIVE INHIBITION OF HERPES SIMPLEX VIRUS TYPE 1-INDUCED CELL FUSION.

Bzik DJ, Person S, Read GS

Biophysics Program, Pennsylvania State Univ., University Park, PA, 16802

Virology; 117(2):504-509 1982

Previous studies have demonstrated that syn mutant-infected cells fuse less well with nonsyncytial virus-infected cells than with uninfected cells, a phenomenon defined as function inhibition. The present study characterizes the kinetics as well as the requirements for expression of fusion inhibition. Initially, the capacity of sparse syn mutant-infected cells to fuse with uninfected surrounding cells was determined throughout infection. Of seven syn mutants examined, including representatives with alterations in two different viral genes that affect cell fusion, all showed an increase in fusion capacity up to 12 hr after infection and a decrease at later times. Fusion inhibition was examined in experiments employing sparse syn20-infected cells which had been incubated to a max fusion capacity; it was shown that surrounding cells infected with KOS, the parent of syn20, began to inhibit fusion by the syn20-infected cells at about 4 hr after infection, and that the max ability to inhibit fusion was attained at about 6 hr after infection. The metabolic blocking agents actinomycin D (RNA), cycloheximide (protein), 2-deoxyglucose, and tunicamycin (glycosylation of glycoproteins) all showed the ability to inhibit the expression of fusion inhibition by KOS-infected cells if added shortly after infection. It is concluded that fusion inhibition is an active process that requires the synthesis of RNA, proteins and glycoproteins. (Author abstract) (17 Refs)

14. CYTOMEGALOVIRUS REPLICATION IN PRIMARY AND PASSAGED HUMAN PLACENTAL CELLS.

Rosenthal LJ, Panitz PJ, Crutchfield DB, Chou JY

Dept. Microbiology, Georgetown Univ. Sch. Medicine and Dentistry, Washington, DC, 20007

Intervirology; 16(3):168-175 1981

Human cytomegalovirus (HCMV) was found to replicate in passaged fibroblastic human first trimester and term placental cells. The time-course of viral DNA replication as well as virus production in these human placental fibroblasts was similar to that in human embryo fibroblast cultures. In contrast, HCMV did not replicate in primary placental epithelioid cells. Continued passage (5 or more) of primary placental epithelioid cells was necessary to convert these cells to a state of permissiveness. The permissive cells were, however, fibroblasts. HCMV DNA replication in passaged placental fibroblastic cells was not affected by treatment with insulin or human chorionic gonadotropin. Furthermore, no replication of HCMV DNA occurred in choriocarcinoma cells, the epithelioid cells derived from cancer of the placenta. These results suggest that epithelial placental trophoblasts, either normal or transformed, were nonpermissive for HCMV. The permissiveness of HCMV infection to secondary placental cells which was observed might be due to the strong selection of fibroblastic cells in vitro. (Author abstract) (21 Refs)

15. EFFECTS OF STEROIDS ON VIRAL INFECTION OF HUMAN BREAST CANCER CELL LINES BY ADENOVIRUS 5.

Chouvet C, Chardonnet Y, Saez S

Centre Leon Berard, 28 rue Laennec, 69372 Lyon Cedex 2, France

J Steroid Biochem; 15:269-274 1981

Effects of steroid hormones, especially estradiol (ES), on the infection of MCF7, a human epithelial cell line established from a metastatic breast adenocarcinoma, by adenovirus 5 were studied. Cytopathy induced by viral infection occurred 24 hr earlier in the presence of 10(-8) M ES. Some differences in the synthesis of viral proteins were detectable at 32 hr, and at 40 hr 78% of cells grown in the presence of hormone were positive vs 44% in the control. Potentiation of viral production is significant after 29 hr of infection and is max from 37 to 48 hr. The quantity of complete infectious particles produced in the control without hormone was very small for low virus concentrations [10 plaque forming units (PFU)/ cell] and increased with the dose of virus used. In the presence of ES, the difference with control was max for low infectious doses. Cells infected in the presence of 10(-9) M ES did not produce more viral particles than controls, but the addition of 10(-8) M ES amplified the number of PFU produced/cell approx 10x. Hormone deletion after infection did not decrease the production of viral particles. Whether the hormone was deleted for 2 or 4 hr before infection, the increase in viral production occurred as if hormone were present. The hormonal effect is apparently steroid specific and requires the corresponding receptors. More viral DNA is synthesized in the presence of hormone and max effect occurs later in the presence of hormone. No evidence was obtained for the synthesis of a protein specific to the hormonal effect, but the kinetics of synthesis were different between the hormone treated and untreated cultures. (26 Refs)

16. ADENOVIRAL HETEROGENEOUS NUCLEAR RNA IS ASSOCIATED WITH THE HOST NUCLEAR MATRIX DURING SPLICING.

Mariman EC, Van Eekelen CA, Reinders RJ, Berns AJ, Van Venrooij WJ

Dept. Biochemistry, Univ. Nijmegen, Geert Grooteplein Noord 21, 6525 EZ Nijmegen, The Netherlands

J Mol Biol; 154(1):103-119 1982

After infection of HeLa cells with adenovirus type 2, virus-specific heterogeneous nuclear RNA is quantitatively associated with a higher ordered structure, the nuclear matrix. Analysis of this matrix-associated RNA by S1 nuclease mapping showed that precursors as well as processed messenger RNAs from the late region L4 were present. By irradiation of intact cells with ultraviolet light, proteins tightly associated with heterogeneous nuclear RNA can be induced to cross-link with the RNA. Characterization of the cross-linked RNA-protein complexes showed that all viral polyadenylated RNAs (precursors, products and processing intermediates) could be cross-linked to two host proteins, earlier found to be involved in the association of host-specific heterogenous nuclear RNA to the nuclear matrix. Our results thus further support the concept that the nuclear matrix may function in the localization and the structural organization of (viral) heterogeneous nuclear RNA during its processing. (Author abstract) (31 Refs)

17. EFFECT OF DELETIONS IN ADENOVIRUS EARLY REGION 1 GENES UPON REPLICATION OF ADENO-ASSOCIATED VIRUS.

Laughlin CA, Jones N, Carter BJ
Lab. Experimental Pathology, Natl. Inst. Arthritis, Diabetes, and Digestive and Kidney Diseases, Bethesda, MD, 20205
J Virol; 41(3):868-876 1982

The growth of adeno-associated virus (AAV) is dependent upon helper functions provided by adenovirus. We investigated the role of adenovirus early gene region 1 in the AAV helper function by using six adenovirus type 5 (Ad5) host range mutants having deletions in early region 1. These mutants do not grow in human KB cells but are complemented by and grow in a line of adenovirus-transformed human embryonic kidney cells (293 cells); 293 cells contain and express the Ad5 early region 1 genes. Mutants having extensive deletions of adenovirus early region 1a (dl312) or regions 1a and 1b (dl313) helped AAV as efficiently as wild-type adenovirus in 293 cells, but neither mutant helped in KB cells. No AAV DNA, RNA, or protein synthesis was detected in KB cells in the presence of the mutant adenoviruses. Quantitative blotting experiments showed that at 20 hr after infection with AAV and either dl312 or dl313 there was less than one AAV genome per cell. In KB cells infected with AAV alone, the unreplicated AAV genomes were detected readily. Apparently, infection with adenovirus mutant dl312 or dl313 results in degradation of most of the infecting AAV genomes. We suggest that at least an adenovirus region 1b product (and perhaps a region 1 a product also) is required for AAV DNA replication. This putative region 1b function appears to protect AAV DNA from degradation by an adenovirus-induced DNase. We also tested additional Ad5 mutants (dl311, dl314, sub315, and sub316). All of these mutants were inefficient helpers, and they showed varying degrees of multiplicity leakiness. dl312 and dl313 complemented each other for the AAV helper function, and each was complemented by Ad5ts125 at the nonpermissive temperature. The defect in region 1 mutants for AAV helper function acts at a different stage of the AAV growth cycle than the defect in the region 2 mutant ts125. (Author abstract) (42 Refs)

18. DISTRIBUTION OF REPLICATING SIMIAN VIRUS 40 DNA IN INTACT CELLS AND ITS MATURATION IN ISOLATED NUCLEI.

Tapper DP, Anderson S, DePamphilis ML
Dept. Pathology, Stanford Medical Sch., Stanford, CA, 94305
J Virol; 41(3):877-892 1982

The maturation of replicating simian virus 40 (SV40) chromosomes into superhelical viral DNA monomers [SV40(I) DNA] was analyzed in both intact cells and isolated nuclei to investigate further role of soluble cytosol factors in subcellular systems. Replicating intermediate [SV40(I) DNA] were purified to avoid contamination by molecules broken at their replication forks, and the distribution of SV40(RI) DNA as a function of its extent of replication was analyzed by gel electrophoresis and electron microscopy. With virus-infected CV-1 cells, SV40(RI) DNA accumulated only when replication was 85 to 95% completed. These molecules [SV40(RI*) DNA] were two to three times more prevalent than an equivalent sample of early replicating DNA, consistent with the rate-limiting step in the separation of sibling chromosomes. Nuclei isolated from infected cells permitted normal maturation of SV40(RI) DNA into SV40(I) DNA when the preparation was supplemented with cytosol. However, in the absence of cytosol, the extent of DNA synthesis was diminished three- to five-fold (regardless of the addition of ribonucleotide triphosphates), with little change in the rate of synthesis during the first minute; also, the joining of Okazaki fragments to long nascent DNA was inhibited, and SV40(I) DNA was not formed. The fraction of short-nascent DNA chains that may have resulted from dUTP incorporation was insignificant in nuclei with or without cytosol. Pulse-chase experiments revealed that joining, but not initiation, of Okazaki fragments required cytosol. Cessation of DNA synthesis in nuclei without cytosol could be explained by an increased probability for cleavage of replication forks. These broken molecules masqueraded during gel electrophoresis of replicating DNA as a peak of 80% completed SV40(RI) DNA. Failure to convert SV40(RI*) DNA into SV40(I) DNA under these conditions could be explained by the requirement for cytosol to complete the gap-filling step in Okazaki fragment metabolism; circular monomers with their nascent DNA strands interrupted in the termination region [SV40(II*) DNA] accumulated with unjoined Okazaki fragments. Thus, separation of sibling chromosomes still occurred, but gaps remained in the terminal portions of their daughter DNA strands. These and other data support a central role for SV40(RI*) and SV40(II*) DNAs in the completion of viral DNA replication. (Author abstract) (56 Refs)

19. ACTIVATION OF SV40 GENOME BY 72-BASE PAIR TANDEM REPEATS OF MOLONEY SARCOMA VIRUS.

Levinson B, Khoury G, Woude GV, Gruss P
Lab. Molecular Virology, NCI, NIH, Bethesda, MD, 20205
Nature; 295(5850):568-572 1982

The simian virus 40 (SV40) 72-base pair (bp) tandem-repeated sequences have a crucial role as an activator element in viral gene expression. We placed the SV40 72-bp repeat with a 72-bp repeat derived from the long terminal repeat (LTR) of cloned Moloney murine sarcoma virus (MSV) DNA. Although there is no detectable sequence homology to SV40, the MSV repeats can substitute functionally for the SV40 repeats and generate a viable virus in monkey kidney cells. (Author abstract) (45 Refs)

20. DNA POLYMERASE REQUIREMENTS FOR PARVOVIRUS H-1 DNA REPLICATION IN VITRO.

Kollek R, Tseng BY, Goulian M
Institut fur Biochemie, Univ. Munchen, Karlstrasse 23, D-8000 Munchen 2, W. Germany
J Virol; 41(3):982-989 1982

An in vitro system using nuclei from parvovirus H-1-infected cells was used to characterize the influence of inhibitors of mammalian DNA polymerases on viral DNA synthesis. The experiments tested the effects of aphidicolin, which is highly specific for DNA polymerase alpha, and 2',3'-dideoxythymidine-5'-triphosphate (ddTTP), which inhibits cellular DNA polymerase in the order gamma greater than beta greater than alpha. Both aphidicolin and ddTTP were inhibitory, indicating that both polymerase alpha and a ddTTP-sensitive enzyme are required for viral DNA synthesis. This was seen more clearly in kinetic measurements, which indicated an initial period of rapid DNA synthesis with the participation of polymerase alpha, followed by a period of less rapid, but more sustained, rate of DNA synthesis carried out by a ddTTP-sensitive enzyme, probably polymerase gamma. One interpretation of the results is that polymerase alpha function in a strand displacement stage of the viral DNA replication mechanism, whereas polymerase gamma serves to convert the displaced single strands back to double-strand replicative form. (Author abstract) (42 Refs)

21. STUDIES ON THE MATERNAL-INFANT TRANSMISSION OF THE HEPATITIS B VIRUS AND HBV INFECTION WITHIN FAMILIES.

Tong MJ, Thursby MW, Lin J-H, Weissman JY, McPeak CM
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:137-147 1981

Results of a study of hepatitis B virus (HBV) infection indicate that the major mode of infection in endemic areas may be maternal-infant transmission, although transmission may also occur by other modes. Many infants carrying hepatitis Bs antigen (HBsAg) develop anicteric CPH and become positive for hepatitis Be antigen. Intrafamilial clustering of HBV infection occurs in certain ethnic groups, regardless of their location. Different infected members of a family may exhibit different clinical syndromes. Spread of HBV may be interrupted by treatment of infants of HBsAg mothers and careful use of HBV vaccine in HBsAg- family members. (11 Refs)

22. PROPAGATION OF HUMAN HEPATITIS A VIRUS IN CELL LINES OF PRIMARY HUMAN HEPATOCELLULAR CARCINOMAS.

Deinhardt F, Scheid R, Gauss-Muller V, Frosner G, Siegl G
Pettenkofer Inst., Pettenkoferstrasse 9a, D-8000 Munich 2, W. Germany
Prog Med Virol; 27:109-113 1981

Successful infection of the hepatoma PLC/PRF/5 cell line with hepatitis A virus (HAV) and detection of HAAg and HBsAg antigens by radioimmunoassay and immunofluorescence are described. HAV also multiplied in HEP 3 B 2.17 cells but could not be grown in HBV-negative Malavu cells. HAV has uncharacteristically slow growth for a supposed enterovirus and has other unique characteristics which may make commercial vaccine production difficult. (11 Refs)

23. TUMOR PROMOTER-STIMULATED SYNTHESIS OF MASON-PFIZER MONKEY VIRUS.

Wunderlich V, Baumbach L, Sydow G
Central Inst. Cancer Res., Acad. Sciences German Democratic Republic, Lindenberger Weg 70/80, DDR-1115 Berlin, E. Germany
J Cancer Res Clin Oncol; 102(3):271-275 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) increases by severalfold the synthesis of Mason-Pfizer monkey virus (MPMV), a type D retrovirus, when the virus is growing in human embryo kidney (HEK) cells. The effect is transient and paralleled by a striking morphological alteration of the cells. The optimal TPA concentration for stimulation is 5 ng/ml. Contrary to infected HEK cells, TPA induces at similar concentrations neither stimulation of MPMV synthesis nor altered morphology in persistently MPMV-infected cells of the continuous human tumor cell line A 204. (Author abstract) (15 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

24. DNA OF HERPESVIRUS PAN, A THIRD MEMBER OF THE EPSTEIN-BARR VIRUS-HERPESVIRUS PAPIO GROUP.

Heller M, Gerber P, Kieff E
Majorie B. Kovler Lab., Univ. Chicago, Chicago, IL, 60637
J Virol; 41(3):931-939 1982

The DNA of herpesvirus pan, a primate B-lymphotropic herpesvirus, shares about 40% well-conserved sequence relatedness with Epstein-Barr virus (EBV) and herpesvirus papio DNAs. Labeled cloned fragments from the EBV recombinant DNA library were cross hybridized to blots of EcoRI, XbaI, and BamHI restriction endonuclease fragments of herpesvirus pan genome. Regions of colinear homology were demonstrated between 6 x 10(6) daltons and 108 x 10(6) daltons in the DNAs. The structural organization of herpesvirus pan DNA was similar to the format of Epstein-Barr virus and herpesvirus papio DNAs. The DNA consists of two domains of largely unique sequence complexity, a segment Us of 9 x 10(6) daltons and a segment UL of 88 x 10(6) daltons. Us and UL are separated by a variable number of tandem repetitions of a sequence IR (2 x 10(6) daltons). There was homology between DNA which mapped at 26 to 28 x 10(6) daltons and 93 to 95 x 10(6) daltons in UL. The terminal reiteration component, TR, of herpesvirus pan DNA and sequences which mapped to the left of 6 x 10(6) daltons and to the right of 108 x 10(6) daltons had no detectable homology with the corresponding regions of Epstein-Barr virus DNA. (Author abstract) (39 Refs)

25. CORRELATION OF THE VIRUS SEQUENCE CONTENT AND BIOLOGICAL PROPERTIES OF CELLS CARRYING THE HERPES SIMPLEX VIRUS TYPE 2 THYMIDINE KINASE GENE.

Minson A, Bell SE, Bastow K
Dept. Pharmacology, Univ. North Carolina, Chapel Hill, NC, 27514
J Gen Virol; 58(part1):127-138 1982

Seven cell lines, transformed to a thymidine kinase-positive phenotype with herpes simplex virus type 2 (HSV-2) DNA fragments, have been examined to determine their virus-specific DNA sequence content. The results are consistent with the reported map position of the HSV-2 thymidine kinase gene. Different cell lines contained different amounts of non-selected virus-specific sequences and this correlated with the ability of some cell lines to compensate for the deficiencies in some temperature-sensitive (ts) mutants of HSV-1 and HSV-2. The cell lines were also examined for their ability to synthesize elevated levels of thymidine kinase in response to infection with a thymidine kinase-negative virus mutant. Of the seven cell lines, two failed to respond to infection in this way, and these cell lines lacked sequences on the upstream side of the kinase gene which were present in the remaining cell lines. (Author abstract) (41 Refs)

26. DNA SEQUENCE OF AN IMMEDIATE-EARLY GENE (IE MRNA-5) OF HERPES SIMPLEX VIRUS TYPE I.

Watson RJ, Vande Woude GF
Lab. Molecular Oncology, NCI, NIH, Bethesda, MD, 20205
Nucleic Acids Res; 10(3):979-991 1982

We describe a 2560 base pair herpes simplex virus Type 1 (HSV-1) DNA sequence containing the entire immediate-early mRNA-5 (IEmRNA-5) gene. The 3' and 5' termini of IEmRNA-5 were mapped within this DNA sequence by single-strand specific endonuclease protection experiments. The IEmRNA-5 gene contains DNA sequences from both the unique (Us) and reiterated (TRs/IRs) regions of the HSV-1 DNA short component and is interrupted by a single intron mapping in TRs/IRs. A search of the transcribed DNA sequence revealed no initiator codon within TRs/IRs. The first ATG was located six bases into Us sequences and this reading frame was open for a further 87 codons. A second longer open reading frame (316 codons) was also observed in the 3' transcribed region. The oligonucleotide sequences adjacent to the IEmRNA-5 termini are discussed in relation to those of the HSV-1 thymidine kinase gene and other genes transcribed by RNA polymerase II. (Author abstract) (35 Refs)

27. A 3' CO-TERMINUS OF TWO EARLY HERPES SIMPLEX VIRUS TYPE 1 MRNAS.

McLauchlan J, Clements JB

Inst. Virology, Univ. Glasgow, Glasgow G11 5JR, Scotland

Nucleic Acids Res; 10(2):501-512 1982

A 3' co-terminus of two early herpes simplex virus type 1 mRNAs has been identified using the nuclease-51 mapping procedure with cloned virus DNA probes. These mRNAs (5.0 kb and 1.2 kb), located within the genome region 0.56-0.60, are unspliced and are transcribed rightwards on the prototype genome orientation. The position of their 3' ends has been located on the virus DNA sequence and lies downstream from the polyadenylation signal 5'-AATAAA-3'. This hexanucleotide sequence also was present in the complementary DNA strand and was shown to be the polyadenylation signal for a leftwards-transcribed late mRNA. The abundance within the cytoplasm of the 5.0 kb and 1.2 kb mRNAs was investigated. Results indicated that these mRNAs were regulated in concert. It is suggested that sequences at the 3' co-terminus may be involved in their regulation. (Author abstract) (25 Refs)

28. GLYCOPROTEIN PROCESSING IN MUTANTS OF HSV-1 THAT INDUCE CELL FUSION.

Person S, Kousoulas KG, Knowles RW, Read GS, Holland TC, Keller PM, Warner SC

618 Mueller Lab., Pennsylvania State Univ., University Park, PA, 16802

Virology; 117(2):293-306 1982

The synthesis of viral-specified glycoproteins, and their appearance on cell surfaces, were compared for cells infected either with syncytial mutants of HSV-1 or with the parental strains from which the mutants were derived. The mutants MP and tsB5, representatives of two different viral genes that affect fusion, were employed in these studies. Cells infected with either mutant gave rise to reduced surface labeling of major viral-specified glycoproteins throughout infection relative to the parental strains. Putative glycoprotein precursors were synthesized in similar amounts throughout infection in mutant and wild-type infected cells. However, during a chase period after a pulse of labeling, fully glycosylated species of glycoproteins accumulated more slowly in mutant than in parent infected cells. This effect was clearly visible early in MP-infected cells and by 9 hr after infection for tsB5-infected cells, and increased thereafter. Apparently the decrease in appearance of glycoproteins on the cell surface of mutant-infected cells is due to a decrease in their rate of processing. (Author abstract) (26 Refs)

29. MUTATIONS IN THE HERPES SIMPLEX VIRUS DNA POLYMERASE GENE CAN CONFER RESISTANCE TO 9-BETA-D-ARABINOFURANOSYLADENINE.

Coen DM, Furman PA, Gelep PT, Schaffer PA
Dept. Microbiology and Molecular Genetics, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
J Virol; 41(3):909-918 1982

Mutants of herpes simplex virus type 1 resistant to the antiviral drug 9-beta-D-arabinofuranosyladenine (araA) have been isolated and characterized. Ara-A-resistant mutants can be isolated readily and appear at an appreciable frequency in low-passage stocks of wild-type virus. Of 13 newly isolated mutants, at least 11 were also resistant to phosphonoacetic acid (PAA). Of four previously described PAA-resistant mutants, two exhibited substantial araA resistance. The araA resistance phenotype of one of these mutants, PAAr5, has been mapped to the HpaI-B fragment of herpes simplex virus DNA by marker transfer, and araA resistance behaved in marker transfer experiments as if it were closely linked to PAA resistance, a recognized marker for the viral DNA polymerase locus. PAAr5 induced viral DNA polymerase activity which was much less susceptible to inhibition by the triphosphate derivative of araA than was wild-type DNA polymerase. These genetic and biochemical data indicate that the herpes simplex virus DNA polymerase gene is a locus which, when mutated, can confer resistance to araA and thus that the herpes simplex virus DNA polymerase is a target for this antiviral drug. (Author abstract) (41 Refs)

30. EXPRESSION OF HERPESVIRUS THYMIDINE KINASE GENE UNDER CONTROL OF EARLY PROMOTER OF SV40.

Pater MM, Pater A, Di Mayorca G, Smiley JR
Dept. Microbiology, New Jersey Medical Sch., Coll. Medicine and Dentistry New Jersey, 100 Bergen St., Newark, NJ, 07103
Virology; 117(2):536-540 1982

A 0.31-kilobase fragment of SV40 DNA containing the early promoter of this virus was isolated. The pX1 plasmid containing the herpesvirus thymidine kinase gene (TK) was cleaved with BglII and SalI to remove the TK promoter. The SV40 DNA fragment was mixed with the TK gene without its promoter and blunt-end ligated after treatment with S1 nuclease. The newly engineered plasmid was used for the transformation of TK-deficient LtA cells to TK phenotype. Blot hybridization experiments show that the plasmid is integrated into high-mol-wt DNA in both of the transformed colonies that we have studied. Also the mRNA in these cells is a hybrid molecule containing both TK and SV40 sequences. (Author abstract) (29 Refs)

31. EFFECT OF METHYLATION ON EXPRESSION OF MICROINJECTED GENES.

Waechter DE, Baserga R
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Proc Natl Acad Sci USA; 79(4,part1):1106-1110 1982

The cloned genes for the simian virus 40 large tumor antigen and for herpes simplex virus (HSV) thymidine kinase (TK) were methylated with EcoRI methylase. The genes were microinjected into the nuclei of TK-deficient (tk-) cells, and expression of the genes was determined by immunofluorescence staining for the simian virus 40 large tumor antigen and by [3H]thymidine incorporation followed by autoradiography for HSV TK. We found that methylation of the simian virus 40 gene, under EcoRI or EcoRI* conditions, resulting in methylation at sites within the gene and in the surrounding sequences, has no effect on expression of the large tumor antigen when the gene is manually microinjected into mammalian nuclei. However, methylation of the HSV tk gene at the two EcoRI sites markedly reduces or abolishes the expression of this gene. Of the EcoRI sites of HSV tk is approx 1.1 kilobases downstream from the 3' end of the gene and is believed to have no regulatory function in the expression of the tk gene. The other EcoRI site is 79 base pairs upstream from the 5' end of the gene and has considerable homology to the regulatory sequence proposed by Benoist, O'Hare, Breathnach, and Chambon. Our results are direct proof that methylation can alter gene expression and also that the effect depends strictly on the sites that are methylated. (Author abstract) (40 Refs)

32. ELECTRON MICROSCOPE MAPPING OF RNA POLYMERASE BINDING SITES ON SV40 DNA.

Vogel F, Scherneck S
Zentralinstitut fur Molekularbiologie, Akademie der Wissenschaften der DDR, DDR-1115 Berlin-Buch, E. Germany
Gene; 16(1-3):331-334 1981

RNA polymerase from Escherichia coli was bound to the genome of simian virus 40 (SV40) after cleavage of the DNA with EcoRI or HpaII restriction enzymes. The enzyme DNA complexes were studied by electron microscopy. Nine binding sites were identified, including five in the 'early' region and four minor sites in the 'late' region of the SV40 DNA. Results suggest that the early region is a strongly conserved part of the SV40 genome. (17 Refs)

33. UNCOUPLING OF SV40 TSA REPLICON ACTIVATION FROM DNA CHAIN ELONGATION BY TEMPERATURE SHIFTS AND APHIDICOLIN ARREST.

Dinter-Gottlieb G, Kaufmann G
Biochemistry Dept., Weizmann Inst. Science, Rehovot 76100, Israel
Nucleic Acids Res; 10(2):763-773 1982

To synchronize SV40 replicons, simian cells infected with a tsA mutant were restricted at 40 C, to complete ongoing replication and returned to 32 C, to activate new replicons in the presence of the DNA chain elongation inhibitor aphidicolin. Upon further incubation at 40 C without the drug, 3H-dT was incorporated into SV40 FI DNA, almost to the extent seen with cells recovered in the absence of the drug. To determine whether DNA synthesis would begin from the origin, following the temperature-shifts-aphidicolin regimen, chains subsequently pulse-labeled with (alpha-32P)dGTP in isolated nuclei were analyzed for size distribution and genomic location. These chains reached up to 300-400 nucleotides in size, unlike the control which featured comparable amounts of label in long chains and Okazaki pieces. The nascent DNA of the drug-treated system could be chased into longer chains, indicating that it was a replicative intermediate; and it hybridized preferentially to an origin proximal fragment of AtuI-restricted SV40 DNA, demonstrating partial replicon synchronization. The data prove that T-antigen activates the SV40 replicon independent of DNA chain elongation and suggest means to study the mechanism of DNA chain priming at the origin. (Author abstract) (30 Refs)

34. TRNA PRECURSOR TRANSCRIBED FROM A MUTANT HUMAN GENE INSERTED INTO A SV40 VECTOR IS PROCESSED INCORRECTLY.

Zasloff M, Santos T, Hamer DH
Genetics and Biochemistry Branch, Natl. Inst. Arthritis, Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD, 20205
Nature; 295(5849):533-535 1982

Functional properties of the human variant initiator transfer (t)RNA gene within an intact cell were assayed by studying its transcription from a simian virus 40 (SV40) recombinant during lytic infection of African green monkey kidney cells. Structure of the SV40-tRNAiMet recombinant (SVtm) used contained a 1.15-kilobase fragment of human genomic DNA harboring a single tRNAiMet gene. Resulting viral stocks were used in the study. Total cytoplasmic and nuclear RNA were recovered from the infected cells and analyzed. Cytoplasmic and nuclear fractions from SVtm-infected cells contained a single low-mol wt species approx 89 nucleotides long. The RNA species accumulating in the SVtm infection was analyzed by classical fingerprinting techniques. The transcript was a precursor of the variant tRNAiMet. Only a preliminary analysis of base modification within the precursor was performed. Hybridization of equal amounts of gel-purified tRNA from SVtm and control infections to filter bound tRNAiMet DNA occurred at approx equal rates and reached max level of hybridization of approx 1% of the input radioactivity. Results indicate that conversion of the mutant precursor to mature tRNA does not occur with any significant efficiency, suggesting that mutations within eukaryotic tRNA genes may be more prevalent than assumed from the limited sequence variation observed in mature tRNA species. (22 Refs)

35. IN VITRO FORMATION OF MULTIMERIC DNA STRUCTURES MEDIATED BY PURIFIED SIMIAN VIRUS 40 CHROMATIN.

Waldeck W, Zentgraf H, Sauer G
Inst. Virus Res., German Cancer Res. Center, 6900 Heidelberg, W. Germany
Proc Natl Acad Sci USA; 79(4,part1):1027-1031 1982

Simian virus 40 chromatin was incubated after purification by sucrose density-gradient centrifugation with various circular double-stranded DNA substrates. Monomeric rings were converted in the presence of Mg to structures possessing a higher degree of complexity. Dimeric catenanes, as well as multimeric linear structures and concatemers, were generated, indicating that recombination events had occurred in vitro involving covalent linkage between different DNA molecules. Furthermore, apparently fused dimeric rings were observed. Their structures suggest that they may be recombination intermediates such as those described in a prokaryotic system. Recombination did not take place between heterologous DNA substrates, as exclusively homologous multimeric DNA structures were observed. (Author abstract) (25 Refs)

36. SIMIAN VIRUS 40 MUTANT WITH TRANSPOSED T-ANTIGEN AND VP1 GENES.

Lazarowitz SG
Dept. Molecular Biology and Genetics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
J Virol; 41(3):1025-1037 1982

A simian virus 40 mutant with T-antigen gene transposed to the late region or the viral genome has been constructed. This transposed molecule directed the synthesis of a full-sized, 92,000-dalton large T antigen in both permissive and nonpermissive cells. This large T antigen functioned in the initiation of viral DNA replication and in the transformation of nonpermissive cells. T-antigen synthesis by this transposed genome had the characteristics of late transcription, thus indicating that functional large T antigen of simian virus 40 is not required for the initiation of late transcription. (Author abstract) (62 Refs)

37. THE NUCLEOTIDE SEQUENCE OF THE GENE FOR PROTEIN IVA2 AND OF THE 5' LEADER SEGMENT OF THE MAJOR LATE MRNAS OF ADENOVIRUS TYPE 5.

van Beveren CP, Maat J, Dekker BM, Van Ormondt H
(c/o van Ormondt) Dept. Medical Biochemistry, Sylvius Laboratories, Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Gene; 16(1-3):179-189 1981

Determination of the base-pair sequence of a portion of the DNA from human adenovirus 5 (Ad5) is presented. The region mapped extends from map position 0.11 (nucleotide 4001) to map position 0.17 (nucleotide 6246, Hind III site). This region corresponds to the region of DNA from adenovirus 2 (Ad2) that encodes the spliced messenger RNA (mRNA) for viral protein (vp) IVa2. The splice point for vpIV2a was determined by annealing the HphI fragment to Ad5 late polyadenylic acid [poly(A)] RNA. The 5' terminus of vpIVa2 was located by hybridizing a 5'-labeled fragment to Ad5 late poly(A) RNA. The 5' terminus was located approx at nucleotide 5840. The splice point was located at nucleotides 5706 and 5427. The 3' terminus of Ad5 DNA was located at nucleotide 4060 by inference from previously reported data on DNA from Ad2. A predicted mol wt (Mr) of 50,873 daltons for the IVa2 protein of Ad5 was calculated based on the DNA nucleotide sequence. The calculated value approximates the previously reported experimentally determined value of 50,000 daltons. The complete DNA sequence of the region mapped, including the 5' leader segment of the major late mRNA of Ad5, is presented. (31 Refs)

38. DIFFERENT MRNAS FROM THE TRANSFORMING REGION OF HIGHLY ONCOGENIC AND NON-ONCOGENIC HUMAN ADENOVIRUSES.

Virtanen A, Pettersson U, Le Moullec JM, Tiollais P, Perricaudet M
Dept. Microbiology, Biomedical Centre, Univ. Uppsala, P.O. Box 581, S-751 23 Uppsala, Sweden
Nature; 295(5851):705-707 1982

Messenger RNA (mRNA) produced from the transforming region of DNA from human adenoviruses was characterized. Adenoviruses were cultured by infection of A549 cells derived from human oat-cell carcinoma. RNA was labeled with 32P. Complementary DNA (cDNA) was prepared from viral mRNA and hybridized to restriction enzyme fragments of viral DNA. The transforming region of viral DNA was characterized by inserting cDNA into pBR322 plasmids and hybridizing to labeled DNA fragments. Characterization of 38 clones containing sequences from the E1B region of the highly oncogenic Ad12 adenovirus showed three classes of mRNA. Ad12 mRNA were compared with mRNA from weakly (Ad5 and Ad7) and non-oncogenic (Ad2) adenoviruses. Results identified two donor sites, designated D1 and D2, and three acceptor sites, designated A1, A2, and A3, in the three classes of mRNA. Donor site D1 was well-conserved and generated a large splice in Ad12 and Ad5. Site D2 was well-conserved and generated a small splice in Ad5, Ad7, and Ad12. Site A1 generated a middle splice in Ad12 not found in Ad5. Site A2 was found in all three viral serotypes. Site A3 was found only in Ad7 and Ad12. Results indicate that mRNA from Ad12 have different structures from mRNA from Ad2, but suggest that the adenoviruses have evolved together. (30 Refs)

39. COMPARISON OF THE POLYOMA VIRUS EARLY AND LATE PROMOTERS BY TRANSCRIPTION IN VIVO.

Jat P, Cowie A, Kamen R
Transcription Lab., Imperial Cancer Res. Fund, P.O. Bos 123, Lincoln's Inn Fields, London, England
Nucleic Acids Res; 10(3):871-837 1982

Polyoma virus DNA was transcribed in the HeLa whole cell extract in vitro system. Early region transcripts with the same 5'-ends as in vivo mRNAs, located 31 -2 bp from 'TATA'-boxes, were synthesized by RNA polymerase II. Sequences sufficient for efficient expression of the early promoter were present in a substitution mutant lacking viral DNA from a position 55bp before the principal cap sites. Late region transcripts were synthesized inefficiently. Only one (at nt5129 -2) of the many late mRNA cap sites functioned as an in vitro initiation point. This was the one 5'-end located 31 -2 bp from a sequence resembling the 'TATA' consensus. The proportion of late to early region RNA poly merase II transcripts decreased dramatically at suboptimal template concentrations. An hypothesis to explain the regulation of late gene expression in vivo based on these results is proposed. Although linear templates were transcribed only by RNA polymerase II, transcripts with the same sense as late mRNAs and 5'-ends at nt5076 -2 were produced from superhelical templates by an alpha-amanitin resistant enzyme. (Author abstract) (52 Refs)

40. DNA SEQUENCE OF THE 5' TERMINUS CONTAINING THE REPLICATION ORIGIN OF PARVOVIRUS REPLICATIVE FORM DNA.

Rhode SL, Klaassen B
Inst. Medical Res. Bennington, Bennington, VT, 05201
J Virol; 41(3):990-999 1982

The nucleotide sequence of the 5' terminus of the parvovirus H-1 was determined. There are two orientations of the 242-base-pair terminal palindrome in native replicative form DNA, one inverted with respect to the other. Adjacent to the terminal palindrome is an AT-rich region that is noncoding and contains a 55-base-pair tandem repeat. The addition mutant of H-1, DI-1, was also sequenced in this region and shown to have three copies of the tandem repeat sequence. Similarly, the related parvovirus H-3 contains only one copy of this repeat sequence. This region contains the replication origin for parvovirus replicative form DNA replication. Some of the implications of these results are discussed. (Author abstract) (37 Refs)

41. DETECTION OF HEPATITIS B VIRUS DNA SEQUENCES IN HUMAN HEPATOCELLULAR CARCINOMA IN AN INTEGRATED FORM.

Brechot C, Pourcel C, Louise A, Rain B, Tiollais P
(c/o Tiollais) Unite de Recombinaison et Expression Genetique, INSERM U 163, Institut Pasteur, 28 Rue du Dr. Roux, F-75724 Paris Cedex 15, France
Prog Med Virol; 27:99-102 1981

The state of viral sequences in human hepatocellular carcinoma (HCC) and human hepatoma cell line (PLC/PRF/5) was analyzed by blot-transfer hybridization with cloned DNA as a probe. Hepatitis B virus (HBV) DNA sequences, both undigested and digested by EcoRI and HindIII endonucleases, were studied by agarose gel electrophoresis. HBV DNA sequences were integrated into the cellular DNA of the three tumor tissues and the hepatoma cell line, providing additional evidence for the causal relationship between HBV chronic infection and HCC. (13 Refs)

42. DNA SEQUENCE RELATIONSHIP OF THE BABOON ENDOGENOUS VIRUS GENOME TO THE GENOMES OF OTHER TYPE C AND TYPE D RETROVIRUSES.

Cohen M, Rice N, Stephens R, O'Connell C
Biological Carcinogenesis Program, Frederick Cancer Res. Facility, Frederick, MD, 21701
J Virol; 41(3):801-812 1982

Baboon endogenous virus (BaEV) is a Type C retrovirus present in multiple proviral copies in the DNA of baboons. Although interspecies antigenic determinants present on reverse transcriptase and gag proteins are shared among all mammalian Type C viruses, no nucleic acid homology between BaEV and other Type C viruses (except RD-114) has been found in conventional liquid hybridization experiments. In this study, we used restriction fragments of cloned BaEV DNA immobilized on nitrocellulose to test for relatedness with [32P]cDNA's of various Type C and Type D viruses. We detected the following distant relationships previously found only through immunological and protein sequencing techniques: (i) eight Type C viral cDNA's and two Type D virus cDNA's were able to hybridize with cloned BaEV DNA; (ii) the eight Type C probes hybridized to restriction fragments spanning most of the BaEV genome, but only RD-114 hybridized to fragments within the 1.9 kilobases at the 3' end of the genome; (iii) the two Type D probes hybridized primarily to fragments within the 1.9 kilobases at the 3' terminus and weakly or not at all elsewhere; and (iv) [32P]cDNA's of several other oncornaviruses exhibited no homology with BaEV DNA. DNA sequence analysis has allowed us to orient the BaEV restriction map with the genetic map at both ends of the genome. Homologies between retroviral cDNA's and BaEV clone restriction fragments could thus be related to specific BaEV genes. These results are discussed relative to previously reported antigenic relatedness of retroviral proteins. The data suggest that BaEV represents an important link in oncornavirus evolution. (44 Refs)

43. COLOBUS TYPE C VIRUS: MOLECULAR CLONING OF UNINTEGRATED VIRAL DNA AND CHARACTERIZATION OF THE ENDOGENOUS VIRAL GENOMES OF COLOBUS.

Birkenmeier EH, Bonner TI, Reynolds K, Searfoss GH, Todaro GJ
Jackson Lab., Bar Harbor, ME, 04609
J Virol; 41(3):842-854 1982

The unintegrated viral DNA intermediates of colobus type C virus (CPC-1) were isolated from infected human cells that were permissive for viral growth. There were two major species of DNA, linear molecules with two copies of the long terminal repeat and relaxed circles containing only a single long terminal repeat. In addition, there was a minor species (approx 10%) composed of relaxed circles with two copies of the long terminal repeat. A restriction endonuclease map of the unintegrated DNA was constructed. The three EcoRI fragments of circular CPC-1 DNA were cloned in the EcoRI site of lambdagtWES-lambdaB and then subcloned in the EcoRI site of pBR322. Using these subgenomic fragments as probes, we have characterized the endogenous viral sequences found in colobus cellular DNA. They are not organized in tandem arrays, as is the case in some other gene families. The majority of sequences detected in cellular DNA have the same map as the CPC-1 unintegrated DNA at 17 of 18 restriction endonuclease sites. There are, however, other sequences that are present in multiple copies and do not correspond to the CPC-1 map. They do not contain CPC-1 sequences either in an altered form or fused to common nonviral sequences. Instead, they appear to be derived from a distinct family of sequences that is substantially diverged from the CPC-1 family. This second family of sequences, CPC-2, is also different from the sequences related to baboon endogenous type C virus that form a third family of virus-related sequences in the colobus genome. (Author abstract) (27 Refs)

IMMUNOLOGICAL STUDIES

44. CYTOLYTIC HUMAN T-CELL CLONES EXPRESSING EPSTEIN-BARR VIRUS SPECIFICITY AND HLA RESTRICTION.

Sethi KK, Stroehmann I, Brandis H
Institut fur Medizinische Mikrobiologie und Immunologie, Universitat Bonn, 5300 Bonn-Venusberg, W. Germany
Immunobiology; 160(3/4):274-288 1981

In an earlier study, we established long-term bulk (uncloned) human T-cell (BTC) cultures which displayed EBV-specific and HLA-restricted lytic activities. The present study demonstrates the feasibility of isolating and propagating clones of CTLs which express EBV specificity and HLA restriction. A total of seven independent cloned cultures derived from two of the initially established BTC cultures were found to exert reproducible, preferential lytic activity towards EBV-infected autologous or HLA-A/B-matched allogenic B blasts. The conclusion that the cloned effectors were exerting EBV-specific and HLA-restricted lysis was supported by the results of cold-target inhibition experiments. In addition, it was found that a monoclonal anti-HLA antibody (W3/62) could effectively block the observed lytic effect Data have been presented suggesting that very early after exposure of B blasts to high multiplicity of EBV, the putative virus-specific component(s) involved in the CTL recognition event is derived directly from the envelope of input EBV. The time required for cell-surface expression of newly synthesized EBV component(s), conferring susceptibility to virus-specific CTLs, was investigated. The results indicate that EBV-infected and papain-treated B blasts acquire optimal susceptibility to the lytic effect of effector T cells 3-4 days following infection. This conversion of infected blasts from the insusceptible states was blocked by the protein-synthesis inhibitor pactamycin only when added immediately and not at 6 hr after papain treatment. On the other hand, papain-treated infected blasts incubated in presence of phosphonoacetic acid, a known inhibitor of EBV-DNA synthesis, were lysable by the effectors. The results imply that EBV-specific envelope protein(s) inserted in target-cell surfaces either 'from without' or de novo synthesized (from within) presumably represent the putative target(s) for virus-specific CTLs in the context of HLA-A/B antigen(s). (35 Refs)

45. CYCLOSPORIN A ABROGATES PROLIFERATION OF T CELLS AND GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTION INDUCED BY EPSTEIN-BARR VIRUS.

Palacios R
Dept. Immunobiology, Wallenberg Lab., Karolinska Institutet, Lilla Frescati, S-1 04 05 Stockholm, Sweden
Immunobiology; 160(3/4):321-329 1981

Cyclosporin A (CYA) promotes the outgrowth in vitro of Epstein-Barr-virus (EBV)-infected cells of immune donors. In the present study, the effects of CYA on the T-cell responses developed in an in-vitro EBV infection were studied. Cyclosporin A, by acting on the responder cells and not on stimulator cells, strongly inhibited the proliferation of T cells normally induced by EBV-infected autologous cells. Moreover, T cells from cultures not exposed to CYA exerted suppression on both alloantigen-induced DNA synthesis and PWM-stimulated immunoglobulin production of autologous peripheral blood mononuclear cells. In contrast, T cells from cultures treated with CYA exhibited significantly less or no suppressor activity as determined in both indicator systems. Finally, CYA abrogated the generation of cytotoxic T cells against EBV-infected autologous cells, whereas non-CYA-treated T cells killed the virus-transformed target cells. Both suppressor and cytotoxic T-cell functions are known to play an essential role in the control of EBV infection by limiting the continuous growth of the virus-infected cells. These results, therefore, strongly suggest that Cyclosporin A promotes the outgrowth of EBV-infected cells by abrogating the T-cell responses to the Epstein-Barr virus. (Author abstract) (23 Refs)

46. RAPID TYPING OF HERPES SIMPLEX VIRUS BASED ON IMMUNOLOGICAL SPECIFICITY OF VIRAL THYMIDINE KINASE AND TYPING ACCORDING TO SENSITIVITY TO IODODEOXYURIDINE.

Gronowitz JS, Kallander CF, Jeansson S, Wallin J
Dept. Medical Virology, Uppsala Univ., Biomedical Center, 751 23 Uppsala, Sweden
J Clin Microbiol; 15(3):366-371 1982

Iododeoxyuridine sensitivity test for discriminating between herpes virus simplex (HVS) Type 1 and 2 strains and typing procedure based on immunological specificity of the thymidine kinase (dTK) present in the first passage of the virus isolate is described. The latter method can be used for typing HVS dTK present in the vesicle fluid, allowing the verification of HVS infection and determination of HVS Type within 5 hr. The possibility of detecting therapy-resistant HVS mutants with this methods is illustrated. (13 Refs)

47. RAPID SEROLOGICAL TECHNIQUE FOR TYPING HERPES SIMPLEX VIRUSES.

Cleveland PH, Richman DD, Oxman MN, Worthen DM
Res. Service, Veterans Administration Medical Center, Univ. California, San Diego, CA, 92161
J Clin Microbiol; 15(3):402-407 1982

A rapid serological technique for typing herpes simplex viruses (HSV) is described. The sensitive 125I-labeled staphylococcal protein immunoassay in which viral antigenes are nonspecifically immobilized on filter paper disks in an immunofiltration manifold was adapted to the typing of HSV isolates. The sensitivity of the technique permits the assay to be carried out with a small number of infected cells and to be performed directly with the primary isolate. (28 Refs)

48. CONFIRMATION OF HERPES SIMPLEX VIRUS TYPE 2 INFECTIONS IN HERPES-LIKE GENITAL LESIONS BY A SIMPLE COMPLEMENT-FIXATION TEST.

Arsenakis M, May JT
(c/o May) Dept. Microbiology, La Trobe Univ., Bundoora, Victoria 3083, Australia
Br J Vener Dis; 58(1):48-51 1982

A complement fixation test with a crude 4-hr herpes simplex virus (HSV)-2-infected human epidermoid carcinoma (HEP-2) cell extract, containing the immediate early HSV-2 antigen (AG-4), was used to distinguish rapidly between HSV-1 and HSV-2 infections. The test was also used to confirm clinically diagnosed genital herpes as HSV-2 infections. Blood samples were obtained from 64 patients (40 women, 24 men; 18-30 yr old) with genital herpes-like lesions and from 23 age- and sex-matched controls. The time-course appearance of complement-fixing antibody to AG-4 in recurrent HSV-2 and in primary HSV-1 and HSV-2 infection is presented. Over the 5-wk period, no anti-AG-4 complement-fixing antibody was detected in patients with HSV-1 infections. The antibody was usually detected 2 wk after a primary infection with HSV-2 and was still present 5 wk later. In 50% of patients with recurrent HSV-2 infections, the anti-AG-4 complement-fixing antibody was detected at 4 days and increased to a max titer at 2 wk after the lesions appeared. No more than 9% of the controls or patients with facial HSV-1 infections had positive results for the antibody. The results indicated that the complement-fixation test can confirm HSV-2 virus infection without isolation of the virus from the herpetic lesion. (13 Refs)

49. AN IMMUNOPEROXIDASE STUDY OF CYTOMEGALOVIRUS MONONUCLEOSIS.

Abramowitz A, Livni N, Morag A, Ravid Z
Dept. Pediatrics, Hadassah-Hebrew Univ. Medical Center, P.O. Box 12,000, Jerusalem, Israel
Arch Pathol Lab Med; 106(3):115-118 1982

Indirect immunoperoxidase method was used to evaluate retrospectively a case of cytomegalovirus (CMV) mononucleosis. Specific rabbit antiserum against CMV was used as primary reagent in routinely prepared paraffin sections of lymph node and in fixed slide preparations of the bone marrow aspirate. Staining specific for CMV antigen was observed in the lymphoid cells of the lymph node in the predominantly T-cell area and in the large lymphoid cells of the bone marrow. Bone marrow lymphoid cells with morphologic characteristics similar to those of the cells positive for CMV antigen showed positive immunoperoxidase reaction with specific rabbit antihuman T-cell serum. The data strongly indicate that CMV antigen was localized predominantly in the cells of lymphoid origin during the acute stage of the CMV mononucleosis; some data also suggest that infected lymphoid cells may be of T-cell origin. An immunoperoxidase technique is advantageous in both diagnosing and evaluating CMV mononucleosis. (Author abstract) (24 Refs)

50. IMMUNE RESPONSES TO VARICELLA-ZOSTER IN THE AGED.

Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ
(c/o Steele), Univ. Arkansas for Medical Sciences, 4301 W. Markham, Slot 512, Little Rock, AR, 72205
Arch Intern Med; 142(2):291-293 1982

Skin test reactivity and in vitro lymphocyte stimulation responses to varicella-zoster (VZ) were examined in a large normal population ranging in age from 6 mo to 93 yr. Waning of cellular immunity, as examined by skin delayed hypersensitivity, began at age 40 yr. Skin test responses to phytohemagglutinin, however, remained positive into the 8th decade of life. In vitro lymphocyte stimulation responses to VZ were usually positive (stimulation index greater than or equal to 2.5) until age 60 yr, after which time levels, as observed with nonimmune individuals, were often demonstrated. Antibody levels, as measured by fluorescent antibody to membrane antigen, remained positive into the 9th and 10th decades of life. This was especially so with a history of reactivation (zoster) VZ infections, while skin test and in vitro responses were rarely positive in those individuals. Thus cellular, as contrasted with humoral, immunity decreases with advancing age, which may account for a propensity to reactivation of VZ virus. (Author abstract) (18 Refs)

51. EXPRESSION OF TWO LATE ADENOVIRUS GENES IS ALTERED BY INTRODUCING ANTIBODIES AGAINST RIBONUCLEOPROTEIN INTO LIVING HELA CELLS.

Lenk RP, Maizel JV, Crouch RJ

Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, 9000 Rockville Pike, Bethesda, MD, 20205

Eur J Biochem; 121(3):475-482 1982

These experiments describe the effect on adenovirus gene expression of transfusing liposome-encapsulated antibodies directed against a 10-S ribonucleoprotein complex into infected HeLa cells. Immunoprecipitation studies demonstrate that this particular serum contains antibodies directed against particles containing U1 RNA and five polypeptides in the mol wt range of 45,000-60,000. The procedure of fusing liposomes successfully treats nearly all the cells in culture, and the transfused material has access throughout the cell. The IgG fraction from this serum is introduced into adenovirus-infected cells shortly before the transition from the early to the late stage of the lytic cycle; 19 hr after fusion the accumulated effects of the antibodies on late virus expression are examined by pulse-labeling cells with radioactive methionine and observing the synthesized proteins. While most late viral genes are expressed normally in treated cells, fiber synthesis is reduced to a very low level and hexon synthesis is reduced twofold. That most viral genes are expressed normally demonstrates that many cell activities (transcription, transport, processing and translation) are minimally affected. The effects on these two genes can be distinguished by varying the concentration of antibody transfused: interference with hexon synthesis occurs at a lower dosage than fiber. A simple interpretation of these results is that the antibody has bound to its antigen and prevented the latter from participating in its role in message processing. (Author abstract) (32 Refs)

52. SPECIES- AND GENUS-SPECIFIC ANTIGENIC DETERMINANTS OF SIMIAN AGENT 12 VP1 AS DEFINED WITH MONOCLONAL ANTIBODIES.

Benton CV, Gilden RV, Shah KV

Bethesda Res. Lab., Inc., 8717 Grovemont Circle, Gaithersburg, MD, 20877

Virology; 117(2):490-495 1982

Monoclonal antibodies were developed against the baboon papovavirus simian agent 12 (SA12). Both SA12-specific and simian virus 40-polyoma Papovaviridae genus-reactive monoclones were isolated. Immunoprecipitation and SDS-PAGE of [35S]methionine-labeled SA12 revealed that all monoclonal antibodies, whether SA12 specific or reactive throughout the genus, were directed against the major capsid protein, VP1, thus directly confirming antigenic polymorphism in this polypeptide. (Author abstract) (24 Refs)

53. CROSS-SECTIONAL AND LONGITUDINAL EPIDEMIOLOGY OF HEPATITIS B IN SENEGAL.

Barin F, Perrin J, Chotard J, Denis F, N'Doye R, Diop Mar I, Chiron JP, Coursaget P, Goudeau A, Maupas P
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonelle, F-37000 Tours, France
Prog Med Virol; 27:148-162 1981

Prior to an immunization program, a field study of seric markers of hepatitis B (HBV) infection was undertaken in the Niakhar district of Senegal. Results of radioimmunoassay for HBsAg, anti-HBs, anti-HBc, and HBeAg-anti-HBe, and anti-hepatitis A virus and passive hemagglutination titer of HBsAg showed a high incidence of HBV; HBV increases sharply from 6 mo to 2 yr old, at which time it is found in 38% of the population. In endemic areas 80% of children 6-7 yr old exhibit at least one HBV seric marker indicating past or present infection acquired either during breast feeding or through contact with siblings, relatives, or other community members during the 2-7 yr old period. (6 Refs)

54. DETECTION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA TISSUES.

Goudeau A, Maupas P, Coursaget P, Drucker J, Chiron JP, Denis F, Diop Mar I, N'Diaye PD
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:77-87 1981

A serological and pathological immunofluorescence study of hepatitis B (HBV) antigens was conducted on liver tissues obtained from 15 patients who died from primary hepatocellular carcinoma (PHC) in Dakar, Senegal, where PHC is obvious upon clinical examination and prevalent in patients in the 30-40 yr age range. Tissue localization of hepatitis B surface antigen and hepatitis B core antigen suggested the following etiological scheme for the HBV role in the genesis of PHC: hepatitis with inflammatory phenomena and necrosis followed by post-necrosis cirrhosis with fibrosis and voluminous regenerative nodules; and PHC evolving from the post-necrotic regenerative nodules. (20 Refs)

55. LOCALIZATION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA.

Nazarewicz-de Mezer T, Slusarczyk J, Krawczynski K, Nowoslawski A
Dept. Immunopathology, Natl. Inst. Hygiene, ul. Chocimska 24, 00-791 Warsaw, Poland
Prog Med Virol; 27:66-76 1981

Studies on the localization of hepatitis B (HBV) antigens by immunofluorescence or immunoperoxidase staining or by fluorochrome- or enzyme-labeled antibodies in cells of patients with hepatocellular carcinoma (HCC) are reviewed. All data obtained by immunomorphological analysis of HCC tissue and indicative of a decreasing potential of expression of HBV antigen with increasing malignancy are compatible with the hypothesis on the oncogenic properties of HBV. (50 Refs)

56. HEPATITIS B VIRAL MARKERS IN PATIENTS WITH CHRONIC HEPATITIS AND WITH PRIMARY HEPATOCELLULAR CARCINOMA IN TAIWAN.

Tong MJ, Chien MC, Lo KJ, Tsai YT, Lee JK
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:60-65 1981

Three prospective studies on the relationship between hepatitis B viral markers and primary hepatocellular carcinoma (PHC) were conducted with patients of Chinese origin at two veterans hospitals. The frequencies of hepatitis B surface antigen (HBsAg) and anti-HBs were determined in 94 chronic hepatitis patients, and the patients' progress was followed for 3 yr. Hepatitis B viral markers were measured by radioimmunoassay in a study involving 102 patients with PHC and HBsAg and anti-HBs were determined in patients with acute viral hepatitis (40), chronic hepatitis (161), and PHC (126). (6 Refs)

57. HEPATITIS B INFECTION IN ALCOHOLIC LIVER DISEASE AND PRIMARY HEPATOCELLULAR CARCINOMA IN FRANCE.

Goudeau A, Maupas P, Dubois F, Coursaget P, Bougnoux P
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:26-34 1981

The prevalence of hepatitis B virus (HBV) markers was studied in 125 asymptomatic heavy drinkers, 163 patients with alcoholic cirrhosis, and 46 patients with histologically proven primary hepatocellular carcinoma. Hepatitis B surface antigen, anti-hepatitis B surface antigen, and anti-hepatitis B core antigen were tested by solid phase radioimmunoassay. Percentages of HBV markers in the three groups were, respectively, 31.2, 54.6, and 21.7, compared to 5% in a control group of 10,000 normal blood donors from the same area in France. (24 Refs)

VIRAL STUDIES IN HUMAN CANCER

58. COMPLEMENT-FIXING ANTIBODY TO EPSTEIN-BARR VIRUS SOLUBLE ANTIGEN IN POPULATIONS AT HIGH AND LOW RISK FOR NASOPHARYNGEAL CARCINOMA.

Levine PH, Ebbesen P, Connelly RR, Das S, Middleton M, Mestre M
NCI, Landow Bldg., ID-12, Bethesda, MD, 20205
Int J Cancer; 29(3):265-268 1982

Greenland Eskimos comprise an ethnic group with one of the highest recorded incidence rates for nasopharyngeal carcinoma in the world. Sera from 625 Eskimos and 73 Danes (Caucasians) living in Greenland, as well as from 62 Danes living in Denmark, were tested for complement-fixing antibody to Epstein-Barr virus (EBV) soluble antigen and, from this study group, 129 donors were matched by age and sex for a study comparing antibody to viral capsid antigen, early antigen, and soluble antigen. Both Eskimos and Danes living in Greenland had significantly higher titers of EBV antibodies than Danes living in Denmark, suggesting that environment was more important than genetics or socioeconomic factors in determining the antibody response to EBV. Age and sex were also factors, higher titers occurring in females and young Eskimos. (Author abstract) (21 Refs)

59. THE AMERICAN BURKITT'S LYMPHOMA REGISTRY: EIGHT YEARS' EXPERIENCE.

Levine PH, Kamaraju LS, Connelly RR, Berard CW, Dorfman RF, Magrath I, Easton JM
Clinical Studies Section, Lab. Viral Carcinogenesis, NCI, Landow Building, Room 1D-12, Bethesda, MD, 20205
Cancer; 49(5):1016-1022 1982

Four hundred twenty-one Americans diagnosed as having Burkitt's lymphoma (BL), 409 from the United States, were studied by the American BL Registry to obtain information about the cause and control of this disease. Of these 421 cases, 256 were confirmed by our pathologists as being morphologically indistinguishable from African BL. A relationship between age and organ involvement was observed; cervical lymph nodes, ileum, and nasopharynx were initial sites of involvement primarily in younger patients. Although the Epstein-Barr virus (EBV) was less frequently associated with American BL than African, a high antibody titer to the EBV capsid antigen was associated with a more favorable prognosis. American BL resembled African BLs time-space clustering, male predominance, and excellent response to chemotherapy. Unlike African BL, however, more patients had involvement of cervical lymph nodes and bone marrow at an early stage of disease. American BL appears to be a more heterogenous disease than African BL. (Author abstract) (28 Refs)

60. SYMPOSIUM ON TUMOURS IN THE TROPICS: HISTORICAL INTRODUCTION, BURKITT'S LYMPHOMA, NASOPHARYNGEAL CARCINOMA AND KAPOSI'S SARCOMA.

Hutt MS
Geographical Pathology Unit, Dept. Histopathology, St. Thomas' Hosp. Medical Sch ., London SE1 7EH, England
Trans R Soc Trop Med Hyg; 75(6):761-765 1981

The geographic distribution of Burkitt's lymphoma (BL) in Africa and New Guinea can be explained by its association with endemic malaria. Heavy Plasmodium falciparum infection in young children suppresses the immune system and enhances lymphocyte proliferation, which in turn may enhance susceptibility to the oncogenic effects of the Epstein-Barr virus (EBV). The age at the time of EBV infection and genetically determined immunologic deficits may also be involved. The sporadic BL of Western nations is usually not associated with EBV. EBV is also implicated in nasopharyngeal carcinoma (NPC). Most of the high-NPC areas are in the tropics of Africa and Asia. Genetic factors seem to be involved. In Malaysia, Singapore, and Hong Kong, the NPC frequency is high in Malays and ethnic Chinese, but low in Indians. Chinese patients with NPC have a previously unidentified second-locus HLA antigen (Sin-2). The NPC frequency is also high among Eskimos, Aleuts, and Alaskan Indians. In this population, the BW40 component of the HLA system is more frequent in NPC patients than in other groups. Kaposi's sarcoma (KS) is rare everywhere in the world except among the black populations of tropical Africa. Its geographic distribution does not seem to be related to ethnic origin, suggesting that environmental factors are the major etiologic determinant. Endogenous, perhaps hormonal factors might account for the male preponderance among KS patients. European and American cases of KS have been reported in immunosuppressed patients. An association of KS with elevated cytomegalovirus antibody titers has been reported in Western countries but not in Africa. (78 Refs)

61. RISK FACTORS FOR CERVICAL CANCER.

Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

Despite a long history of research into the epidemiology and biology of cervical carcinoma, a definitive statement about its probable causes still remains elusive. This review recognizes the population based data on high and low risk groups and summarizes the findings from numerous case-control studies which associated with cervical cancer. Although vigorously pursued, an increased risk from oral contraceptives has not been convincingly demonstrated. A variety of venereally transmitted organisms appear to be frequent cohabitants with cervical neoplastic cells. *Herpesvirus* type 2 still remains the prime suspect in the complex pathogenesis of cervical neoplasia. Clinical findings, biological characteristics of the virus, serological studies and interactions of host cells and viral particles continue to stimulate the most intensive investigative efforts. (Author abstract) (69 Refs)

62. UPDATE ON THE RELATION OF HERPESVIRUS HOMINIS TYPE II TO CARCINOMA OF THE CERVIX.

Fish EN, Tobin SM, Cooter NB, Papsin FR
Div. Infectious Diseases, Hosp. for Sick Children, 555 Univ. Ave., Toronto, Ontario M5G 1X8, Canada
Obstet Gynecol; 59(2):220-224 1982

Animal studies are described that investigate which cofactors influence the progression of herpesvirus hominis Type II (HVH-II)-induced atypia of the cervical epithelium to malignancy. Results indicate that neither chemical nor physical factors markedly affect typical development. However, sperm factors are implicated in influencing this atypical development. These data are considered in relation to the etiologic role of HVH-II in carcinoma of the cervix. (Author abstract) (12 Refs)

63. ADENOVIRUS-RELATED RNA SEQUENCES IN HUMAN NEUROGENIC TUMOURS.

Ibelgaufts H, Jones KW, Maitland N, Shaw JF
Institut fur Biochemie, Universitat Munchen, Karlstr. 23, D-8000 Munchen 2, W. Germany
Acta Neuropathol (Berl); 56(2):113-117 1982

A highly sensitive in-situ hybridization technique was used to detect adenovirus-related nucleic acids in 44 human neurogenic tumors. 3H-Labeled tumor virus DNA probes were derived from human adenovirus Type 2 and 12 (Ad2 and Ad12, respectively), bovine adenovirus Type 3 (BAd3), and avian adenovirus CELO. RNA sequences related to the adenovirus DNA probes used were not found in 10 tumors, three of which contained DNA that hybridized to Ad2 DNA only, 7 to Ad12DNA only, and 3 with BAd3 DNA only. Four tumors were positive for Ad2/Ad12 and three for Ad12/BAd3 simultaneously. Adenovirus-related RNA sequences were found in 2/3 astrocytomas, 2/4 metastatic carcinomas of the brain, 0.23 ependymomas, 2/2 glioblastomas. 1/1 secondary melanomas, 5/7 meningiomas, 4/4 neurinomas, 1/2 oligodendrogliomas, 0/1 pituitary chromophobe adenoma, and 1/1 rhabdomyosarcoma. No avian CELO virus-related RNA was detected in any of the tumors. No hybridization with viral DNA probes was observed in non-neoplastic control tissues. Thus, most brain tumors studied contained adenovirus-related material, predominantly RNA related to human adenovirus type 12. The finding of adenovirus-related RNA in 62% of the tumors tested is a lower estimate and their presence may reflect a viral involvement in the pathogenesis of these tumors. (18 Refs)

64. DNA VIRUSES AND BRAIN TUMOURS.

Ibelgaufts H
Chemisches Laboratorum, Institut fur Biochemie, Universitat Munchem, Karlstrasse 23, 800 Munchen 40, West Germany
Trends Neurosci; 5(1):16-20 1982

Evidence for viral involvement in pathogenesis of some human neurogenic tumors is reviewed. In the case of neurogenic tumor models, direct injection of the virus into the brain eliminates the potential for the host to clear the virus by the immune system. However, certain viruses, such as JCV human papovavirus and adenovirus type 12, can be used to induce intracerebral neoplasms by host infection other than intracerebral injection. Some human viruses (ie human adenovirus type 12 and human papovavirus JCV) are oncogenic both in rodents and in higher primates, however reasons for the differences in oncogenic potential between the various adenovirus serotypes is not known. Locations of the intracellular virus in DNA sequences have not been clearly defined, although some studies indicate that certain viral genes are only found at a limited number of sites; gene cloning techniques should help to evaluate the cellular sites of viral integration and their functions. Other studies suggest that viral genes are essentially fixed in the DNA sequence in virus-induced tumors. However, integrated viral genomes may be lost from transformed cells under certain circumstances. Presence of virus-specific RNA in virus-induced tumor cells is demonstrated by the presence of the so-called tumor(T)-antigen. Etiology of human neurogenic neoplasms is not clear, and proof of a viral etiology of human tumors must largely be circumstantial, yet there are observations that may point to tumor-virus involvement (eg adenovirus) in the pathogenesis of human neurogenic neoplasms. (15 Refs)

65. PAPOVAVIRUS-RELATED RNA SEQUENCE IN HUMAN NEUROGENIC TUMOURS.

Ibelgaufts H, Jones KW
Institut fur Biochemie, Universitat Munchen, Karlsstr. 23, D-8000 Munchen 2, W. Germany
Acta Neuropathol (Berl); 56(2):118-122 1982

Thirty-three human brain tumors were investigated by a sensitive in-situ hybridization technique for the presence of SV40-, BKV-, HDV-, and BPV1-related RNA sequences. Twenty tumors did not contain RNA sequences related to any of the viral DNA probes. BPV1-and HDV-related RNA were not detectable in any of the tissues tested. SV40-related RNA were found in 1/1 angiofibroma, 1/6 astrocytomas, 2/4 intracerebral carcinomas, 1/1 intracranial melanoma, 3/7 meningiomas, 2/4 neurinomas, and 1/2 oligodendrogliomas. Ten of 11 tumors gave positive hybridization with SV40 DNA probe simultaneously hybridized with adenovirus DNA probes. Only 10 tumors hybridized simultaneously with SV40 DNA contained adenovirus-related RNA. Two typical examples of positive hybridization with SV40 DNA in a recurrent meningioma are presented. Almost all cells in the two sections of the same tumor are labeled. BKV-related RNA was detectable in one neuroblastoma of the kidney, but was absent from all brain tumors tested. Tissues derived from the bulbus olfactorius, nervus opticus, cerebellum, cerebrum, and a non-neoplastic spinal cord cyst did not contain any detectable amounts of papovavirus-related nucleic acids. Hybridizations with DNA from bacteriophage alpha and bacterial plasmid pBR322 on tumor and non-neoplastic tissues were all negative. (41 Refs)

66. NEW DEVELOPMENTS IN THE FIELD OF VIRUSES IN LIVER DISEASE.

Buffet C
Service d'hepatologie et de gastro-enterologie, hopital Bicetre, 78, rue du General-Leclerc, 94270 Kremlin-Bicetre, France
Rev Prat; 31(59):4251-4254 1981

Hepatitis A; the significance of hepatitis B virus (HBV) markers, HBV marker in alcoholics, HBV and carcinogenesis, and non-A, non-B (NANB) hepatitis virus are discussed. HBV antigens and antibodies (antibodies to HBV surface and core antigens and those related to viral replication) are discussed in relation to the diagnosis of hepatitis B. HBV markers are elevated in alcoholic populations (40%) as compared with normal blood donors (10%). In most alcoholics, HBV markers indicative of former, non-developing HBV infection are observed. The role of HBV in cirrhosis is discussed. Integration of HBV DNA in the cellular genome of hepatoma tissue has been demonstrated. Epidemiologically, geographic zones with a high incidence of hepatitis are strictly superimposable over zones with a high incidence of hepatomas. Patients positive for HBV antigens with or without cirrhosis show a higher incidence of liver neoplasms. Although other factors are involved in tumorigenesis in the liver, HBV is directly involved in the development of hepatomas. Identification, transmission, and characteristics of NANB hepatitis virus and resultant infection are described. (13 Refs) (In FRE)

67. NATURAL ANTIBODIES TO HUMAN RETROVIRUS HTLV IN A CLUSTER OF JAPANESE PATIENTS WITH ADULT T CELL LEUKEMIA.

Robert-Guroff M, Nakao Y, Notake K, Ito Y, Sliski A, Gallo RC
Dept. Cell Biology, Litton Bionetics, Inc., Kensington, MD, 20895
Science; 215(4535):975-978 1982

Human T cell lymphoma leukemia virus (HTLV) is a human retrovirus (RNA tumor virus) that was originally isolated from a few patients with leukemias or lymphomas involving mature T lymphocytes. Here we report that the serum of Japanese patients with adult T cell leukemia, but not the serum of tested normal donors, contains high titers of antibodies to HTLV. These observations, together with data from Japan showing that adult T cell leukemia is endemic in southwest Japan, suggest that HTLV is involved in a subtype of human T cell malignancy, including Japanese adult T cell leukemia. (Author abstract) (22 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

68. PYROPHOSPHATE ANALOGUES AS INHIBITORS OF DNA POLYMERASES OF CYTOMEGALOVIRUS, HERPES SIMPLEX VIRUS AND CELLULAR ORIGIN.

Eriksson B, Oberg B, Wahren B
Dept. Antiviral Chemotherapy, Res. and Development Lab., Astra Lakemedel AB, Sodertalje, Sweden
Biochim Biophys Acta; 696(2):115-123 1982

Several pyrophosphate analogues have been compared for their ability to inhibit the activities of isolated cytomegalovirus (CMV) DNA polymerase, herpes simplex virus Type 1 (HSV 1) DNA polymerase and calf thymus DNA polymerase alpha. The most effective inhibitors were phosphonoformate and phosphonoacetate. Although not identical, the structural requirements for compounds inhibitory to CMV and HSV-1 DNA polymerase were specific, with two negatively charged groups in close vicinity. The CMV DNA polymerase was more susceptible to certain phosphonoacetates containing bulky hydrophobic alpha-substituents than was the HSV-1 DNA polymerase. No example of the converse preference was found. The inhibition of CMV DNA polymerase by phosphonoformate, hypophosphate, alpha-hydroxyphosphonoacetate and alpha-nonylphosphonoacetate was linear non-competitive with the deoxyribonucleoside triphosphates as variable substrates.

Phosphonoformate, phosphonoacetate, and to a lesser extent alpha-hydroxyphosphonoacetate, carbonyldiphosphonate and alpha-nonylphosphonoacetate also inhibited the focus formation by CMV in cell-culture. (Author abstract) (33 Refs)

69. INTRAVENOUS ACYCLOVIR TO TREAT MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTION AFTER MARROW TRANSPLANTATION. A DOUBLE-BLIND TRIAL.

Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, Meyers JD
(c/o Meyers), Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Ann Intern Med; 96(3):265-269 1982

Acyclovir, a new antiviral agent, was compared to a placebo in a randomized double-blind trial of treatment for culture-proven herpes simplex virus infection after marrow transplantation. Patients received either intravenous acyclovir at 750 mg/m2 body surface area per day or a placebo for 7 days. Thirteen of 17 patients given acyclovir had a beneficial response as compared with 2 of 17 given the placebo (p less than 0.01). The duration of positive cultures was shorter among acyclovir recipients (3 vs 17 days, p less than 0.00005). Also shorter were the median days to resolution of pain (10 vs 16 days, p = 0.03), to crusting of lesions (7 vs 14 days, p = 0.01), and to total healing (14 vs 28 days, p = 0.03). No acyclovir toxicity was observed. Recurrent infection was common. Acyclovir provided significant antiviral and clinical efficacy without toxicity in highly immunosuppressed patients but had no effect on virus latency. (Author abstract) (28 Refs)

70. ACYCLOVIR FOR CHRONIC MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTION IN IMMUNOSUPPRESSED PATIENTS.

Straus SE, Smith HA, Brickman C, De Miranda P, McLaren C, Keeney RE
Medical Virology Section, LCI, NIAID, NIH, Building 10, Room 11-N-113, Bethesda, MD, 20205
Ann Intern Med; 96(3):270-277 1982

Over 25 episodes of severe chronic and recurrent mucocutaneous herpes simplex virus infections in five immunodeficient patients were successfully treated with intravenous or oral acyclovir treatment. Acyclovir was shown to inhibit viral shedding rapidly, to be well tolerated, and to permit the complete healing of lesions. As expected, a course of acyclovir did not prevent later recurrences of the herpes virus infections. However, symptomatic recurrences were successfully suppressed during long (up to 65-day) courses of oral acyclovir. (Author abstract) (23 Refs)

71. THE HUMAN INTERFERON SYSTEM.

Berman B, Frankfort HM
Dept. Dermatology, Mount Sinai Sch. Medicine, 1 Gustave L. Levy Place, New York, NY, 10029
Int J Dermatol; 21(1):12-18 1982

Clinical uses of interferon (IF) in dermatology are reviewed. IF inhibits both DNA- and RNA-containing viruses, as well as nonviral intracellular organisms. The immunomodulatory effects of IF on phagocytosis, histamine, prostaglandin E, antibody dependent cell-mediated cytotoxicity, natural killer lymphocytes, and mitogen activation of lymphocytes are discussed. Clinical studies of IF in cases of herpes zoster, varicella, herpes simplex, vaccinia, congenital rubella, condylomata acuminata and malignant melanoma are discussed. (85 Refs)

72. PREPARATION, EXAMINATION AND CLINICAL APPLICATION OF HUMAN UMBILICAL CORD BLOOD LEUKOCYTE INTERFERON.

Sun M, Pu X, Cheng J, Qiu F, Shao L, Liu J
Beijung First Infectious Diseases Hosp., Beijing, People's Republic of China
Zhonghua Weishengwuxue He Mianyixue Zazh; 1(3):217-220 1981

Interferon was isolated and purified from human cord blood induced with Newcastle disease virus. After passing tests for pyrogens, toxicity, residual virus, activity and physical properties, this interferon was clinically used (per im) to treat chickenpox, herpes zoster, hepatitis B and encephalitis B. It had marked activity on chickenpox and herpes zoster, some effect on chronic active hepatitis B, but no effect on encephalitis B. No significant side toxic or side effects were observed. (5 Refs) (In CHI)

73. PROGRESS IN LABORATORY AND CLINICAL RESEARCH ON ANTIVIRAL DRUGS.

Zheng M, Shi Z
Dept. Microbiology, Jiangxi Medical Coll., Jiangxi Province, People's Republic of China
Yaoxue Tongbao; 16(6):38-43 1981

Although vaccines have been developed during the past few decades for controlling numerous viral infections (small pox, measles, encephalitis B, rabies, and others), preventive and treatment methods for many types of virus infections, such as those casued by rhinoviruses, coronaviruses, influenza viruses, parainfluenza viruses, hepatitis viruses, and herpes simplex virus, still are lacking. Development of antiviral drugs during the past two decades is reviewed, with special reference to research performed in China using traditional Chinese drugs. Dozens of such drugs are listed, some of which had been found to be active against numerous virus strains in vitro. Other antiviral agents reviewed include adamantanamine, adamantane methylamine, rifampicin, streptovaricin, distamycin, interferon, interferon indu cers, moroxydine, ribavirin, 2-(alpha-hydroxybenzyl)-benzimidazole, idoxuridine, cytosine arabinoside and methisazone. Some of these agents also have antitumor activities. Cultivation of viruses on animal and human cell lines for antiviral drug screening is described. (21 Refs) (In CHI)

74. MECHANISM OF INTERFERON ACTION. DIFFERENTIAL EFFECT OF INTERFERON ON THE SYNTHESIS OF SIMIAN VIRUS 40 AND REOVIRUS POLYPEPTIDES IN MONKEY KIDNEY CELLS.

Daher KA, Samuel CE
(c/o Samuel) Section Biochemistry and Molecular Biology, Univ. California, Santa Barbara, CA, 93106
Virology; 117(2):379-390 1982

The effect of interferon (IFN) treatment on the synthesis of viral proteins was examined in BSC-1 monkey kidney cells singly and doubly infected with simian virus 40 (SV40) and reovirus. The pattern and amount of SV40 T antigen and reovirus lambda, mu, and sigma polypeptide synthesis was comparable in singly and doubly infected cells in the absence of IFN treatment. As determined by Yakobson et al and Kingman and Samuel SV40-specific RNA synthesis is inhibited by treatment of cells with IFN before infection, but is not inhibited by IFN treatment after infection. IFN treatment initiated before infection inhibited the synthesis of both SV40 T antigen and reovirus polypeptides. However, SV40 T antigen synthesis was not inhibited in SV40 wt or tsA mutant-infected cells when treated with monkey kidney or human leukocyte IFN after infection. By contrast, reovirus polypeptide synthesis was markedly inhibited in BSC-1 cells treated with IFN after SV40 infection and superinfected with reovirus. SV40 infection did not rescue reovirus polypeptide synthesis from the inhibitory action of IFN, and reovirus infection did not alter the resistance of SV40 T antigen synthesis to IFN in cells IFN-treated after SV40 infection. Total cellular protein synthesis was not significantly affected by IFN treatment. These results suggest that the interferon-induced inhibitor(s) of protein synthesis discriminate between SV40 and reovirus mRNAs; the translation of SV40 mRNA, like most cellular mRNAs, is not affected under conditions where the IFN-induced inhibitor(s) significantly affect the translation of reovirus mRNA. (Author abstract) (40 Refs)

GENERAL REVIEWS

75. HUMAN CANCERS AND HUMAN VIRUSES.

Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

The connection between human cancers and human viruses is reviewed. Evidence of malignancies attributable to DNA viruses, similar to those of animals, is growing. A type of human leukemia retrovirus, the human T-cell leukemia virus, has been isolated. Hepatitis B virus has been shown to be of primary hepatocellular carcinoma and Epstein-Barr virus the cause of Burkitt's lymphoma and nasopharyngeal carcin oma; cytomegalovirus may be implicated in Kaposi's sarcoma and human papillomaviruses may cause skin cancer. To be implicated in oncogenesis, a virus should be found in tumor cells and be capable of transforming normal cells of the same species in vitro and inducing tumors in studies with animals. Human T-cell leukemia virus has been shown to be infectious when cultivated with human umbilical cord leukocytes, transforming them into virus-producing lines. Epstein-Barr virus causes disease only rarely on primary infection in childhood, but in adolescence or adult life it gives rise to infectious mononucleosis. Hepatitis caused by hepatitis B virus can be followed by chronic active hepatitis and cirrhosis and is a suspected cause of primary hepatocellular carcinoma. Malignant change has been reported in laryngeal papillomas, in genital warts, and in epidermodysplasia verruciformis. Factors other than viruses which influence malignant transformation are the genetic constitution and immune state of the patient. The virus-cell relation is not simple. (29 Refs)

76. GENITAL HERPES SIMPLEX: CONCEPTS AND TREATMENT.

Raab B, Lorincz AL
Univ. Chicago, 950 E. 59th St., Box 409, Chicago, IL, 60637
J Am Acad Dermatol; 5(3):249-263 1981

The frequency of genital herpes (GH) infections is rising sharply. The etiologic organism is herpes simplex virus type 1 or 2; infections may be primary or recurrent. Epidemiology, characteristics of herpes simplex viruses, immunological aspects, clinical manifestations, and treatment are presented. The major complications of GH are psychological burdens, neonatal herpes infections, and possible increased risk of cervical cancer. (114 Refs)

77. HERPES SIMPLEX VIRUS: CLINICAL SYNDROMES AND CURRENT THERAPY.

Rand KH
Div. Infectious Diseases, Univ. Florida, Box J-277 JHMHC, Gainesville, FL, 32610
Compr Ther; 8(2):44-50 1982

Herpes simplex virus (HSV) is discussed with respect to the primary infection, recurrent disease, latency, laboratory diagnosis, specific syndromes and their treatment, and its association with cancer. After the initial infection, HSV-1 or HSV-2, or both, persists for life in the sensory ganglia. Local recurrences occur on the skin yr after yr. Both HSV-1 and-2 have been shown to transform cultured cells and to cause cancer in animals. There is no reproducible, direct evidence that HSV-1 and-2 caused cancer in vivo, although HSV antigens and antibodies have been found in human tumors and patients with cancer. (14 Refs)

78. INFECTIOUS MONONUCLEOSIS.

Dorchy H
Departement Universitaire de Pediatrie, Hopital Saint-Pierre, Bruxelles, Belgium
Rev Med Brux; 2(10):977-985 1981

The etiology, physiopathology, and oncogenicity of Epstein Barr virus and the diagnosis, treatment, and prevention of EBV-induced infectious mononucleosis (IM) are discussed. EBV specifically infects B-lymphocytes and also nasopharyngeal epithelial cells. In vivo or in vitro, EBV can inactivate lymphocytes and provoke their lymphoblastic transformation to establish a continuous line of lymphoid cells. Carcinogenic properties of EBV include its ability to produce lymphoblastic transformation, to integrate its viral genome into host cell, and the persistance of a latent infection. EBV is associated with two malignant tumors: Burkitt's lymphoma (BL) and nasopharyngeal cancer (NPC). BL occurs mainly in children 2-14 yr, attacks the maxilla preferentially but may also involve the abdomen or lymph nodes, and results from the uncontrolled division of a clone of B lymphocytes containing EBV genome. In EBV-related NPC, epithelial cells carry the EBV genome. Genetic and environmental risk factors for NPC are described. Topics discussed in relation to IM include the following: epidemiology, clinical signs (polyadenopathies, angina, splenomegaly, hepatomegaly, edema, and skin eruptions), rare manifestations of EBV infections, complementary examinations, development, and prognosis. (48 Refs) (In FRE)

OTHER RELATED STUDIES

79. EPSTEIN-BARR VIRUS RECEPTOR EXPRESSION IS CORRELATED TO CELL CYCLE PHASE.

Wells A, Steen HB, Godal T, Klein G
Box G, Brown Univ. Sch. Medicine, Providence, RI, 02912
J Recept Res; 2(3):285-298 1981

Fluorescent isothiocyanate (FITC)- conjugated virions was directly absorbed by Epstein-Barr virus (EBV), incubated with Raji, Daudi, or YAC cell lines, and for DNA content determination were stained with propidium iodide. FITC binding and labeled DNA were simultaneously measured by flow cytometry. EBV receptor was present throughout the whole cell cycle, but its level of expression increased significantly in both G1 and G2/M phases, but not in S phase. The increase in G1 was greater than in the other phases. The receptor level on the live cells increased directly with cell size; the rate of increase, determined as the receptor density, was inversely correlated with cell size. Early in G1 cells seem to synthesize rapidly the EBV receptor to increase the structure's density. This observation may have in vivo implications in relation to the timing of synthesis after initial cell stimulation. (29 Refs)

80. PROBLEMS POSED BY VACCINATIONS AGAINST VIRUSES OF THE HERPES GROUP.

Rickaert F, Thiry L
Institut Pasteur du Brabant, Universite Libre de Bruxelles, Bruxelles, Belgium
Rev Med Brux; 2(10):909-915 1981

Problems associated with immunization against herpes simplex virus, varicella virus, and cytomegalovirus, three viruses which exhibit latency periods and carcinogenic potentials, are described. Herpes simplex virus is considered in relation to cervix neoplasms. Protection against herpes zoster is particularly important in subjects immunocompromised due to neoplasms, leukemia, or high-dose steroid trea tment. (22 Refs) (In FRE)

81. ASCENDING HERPETIC ENDOMETRITIS.

Schneider V, Behm FG, Mumaw VR
Medical Coll. Virginia, Box 453, Richmond, VA, 23298
Obstet Gynecol; 59(2):259-262 1982

Two cases of herpetic endometritis are reported. In both patients, the disease developed from documented herpetic cervicitis via transcervical ascension. One patient recovered spontaneously. Generalization and death occurred in the other patient, a renal transplant recipient treated with immunosuppressive agents. The histologic features of herpetic endometritis are illustrated. Intranuclear inclusions and ground-glass nuclei were found in endometrial glandular and stromal cells. Focal necrosis was prominent. Herpetic virus particles were demonstrated by electron microscopy in both cases. Ascending herpetic endometritis is a rare complication of a common disease. In patients with deficiencies of the immune system, herpetic endometritis may represent the initial step toward dissemination and warrants particular attention. (Author abstract) (25 Refs)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. DIFFERENTIATION OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 BY SENSITIVITY TO (E)-5-(2-BROMOVINYL)-2'-DEOXYURIDINE.

Mayo DR
Virology Lab., Veterans Admin. Medical Center, West Haven, CT, 06516
J Clin Microbiol; 15(4):733-736 1982

Use of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) sensitivity as a marker was compared with a selective cell culture system which has been used routinely for typing herpes sim-

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plex virus (HSV) strains. Incorporation of BVDU directly into the culture media of cells inoculated with clinical specimens suspected of containing HSV resulted in a reduction of plaque formation in 23 HSV-1 isolates varying from 2.00-3.66 log10, while the plaque-forming ability of the HSV-2 strains was unaffected. BVDU used in this manner allowed for the presumptive identification of HSV types. (8 Refs)

2. IDENTIFICATION OF DNA VIRUSES BY MEMBRANE FILTER HYBRIDIZATION.

Stalhandske P, Pettersson U
Dept. Microbiology, Biomedical Center, Univ. Upssala, S-751 23 Uppsala, Sweden
J Clin Microbiol; 15(4):744-747 1982

A procedure which allows DNA from a roller tube culture to be immobilized on nitrocellulose filters and the subsequent identification of the viral nucleic acids in the sample through molecular hybridization is described. Detection of herpes simplex virus (HSV) DNA in infected cells by hybridization is described and different methods for immobilizing DNA from infected cells are discussed. The time course of HSV infection is presented. Results indicate that it is possible to discriminate between HSV types 1 and 2 in a simple way. (15 Refs)

3. NEW WAY TO ISOLATE SIMIAN VIRUS 40 NUCLEOPROTEIN COMPLEXES FROM INFECTED CELLS: USE OF A THIOL-SPECIFIC REAGENT.

Boyce FM, Sundin O, Barsoum J, Varshavsky A
(c/o Varshavsky) Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
J Virol; 42(1):292-296 1982

A new method for the isolation of simian virus 40 nucleoprotein complexes from nuclei of lytically infected cells is described. The method is based on the addition of a thiol-specific reagent, 5,5'-dithiobis(2-nitrobenzoic acid), to lysis and extraction buffers. By inhibiting an uncoating activity during simian virus 40 extraction, 5,5'-dithiobis(2-nitrobenzoic acid) allows the use of efficient extraction buffers, such as ones containing Triton X-100 and EDTA, for the isolation of native simian virus 40 minichromosomes and virion-type structures. Use of the method is illustrated by following encapsidation of simian virus 40 minichromosomes in a pulse-chase experiment. Since 5,5'-dithiobis(2-nitrobenzoic acid) is an inhibitor of many different enzymes, the 5,5'-dithiobis(2-nitrobenzoic acid) extraction technique may be useful for the isolation of not only papovaviruses but also other viruses and possibly cellular chromatin. (Author abstract) (16 Refs)

4. GROUPING OF ADENOVIRUSES AND IDENTIFICATION OF RESTRICTION ENDONUCLEASE CLEAVAGE PATTERNS OF ADENOVIRUS DNAS USING INFECTED CELL DNA: SIMPLE AND PRACTICAL METHODS.

Suzuki N, Ueno T, Yamashita T, Fujinaga K
Dept. Ophthalmology, Sapporo Medical Coll., S-1, W-16, Chuo-ku, Sapporo, Hokkaido 060, Japan
Microbiol Immunol; 25(12):1291-1301 1981

Simple and practical methods are described for determination of grouping of adenoviruses and identification of viral DNA cleavage patterns, using infected cell DNA. Grouping of adenovirus DNAs by means of infected cell DNA was performed with the spot hybridization technique. Results were similar whether viral or infected cell DNA was used. Restriction endonuclease cleavage patterns could be obtained by Southern blot hybridization, using infected cell DNA. The method was very sensitive and permitted identification of the cleavage pattern of the viral DNA of the inoculum by means of DNA extracted from infected cells at a stage when cytopathic effect was undetectable. Ethidium bromide staining of gels without Southern blot hybridization permits precise detection of the endonuclease cleavage pattern of viral DNA, in spite of background staining due to cellular DNA. However, the ethidium bromide staining procedure required about 100-fold more infected cells than the Southern blot procedure. The preparation of infected cell DNA used in these procedures was technically much easier than that of viral DNA. Only small numbers of infected cells are required so that many isolates may be investigated with ease. (18 Refs)

5. THE STRUCTURE AND FUNCTION OF A MEMBRANE GLYCOPROTEIN ENCODED IN THE ADENOVIRUS GENOME.

Persson H, Philipson L

Dept. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden

Protides Biol Fluid Proc Colloq; 29:97-100 1982

A glycoprotein encoded in the adenovirus genome interacts with the heavy chain of transplantation antigens. Sequence analysis of the E3/16,000 mol wt precursor protein obtained from adenovirus messenger RNA revealed a signal sequence in the N-terminal end and a hydrophobic sequence in the C-terminal end. Two sites are available for addition of carbohydrate to the side chains. It is now possible to identify the region which specifically interacts with HLA in human cells. (5 Refs)

6. CHILDREN'S BRAIN TUMOUR CELLS PRODUCE RNA PARTICLES WITH INCOMPLETE RETROVIRUS CHARACTERISTICS.

Thorne HJ, Jose DG, Adams FC, Coelen RJ, Whitehead RH, Klugg G

Clinical Immunology and Immunogenetics Unit, Cancer Inst., Melbourne, Victoria, Australia

Oncology; 39(3):156-162 1982

Short-term cultures of cells from human brain tumors have been reported to synthesize RNA particles of density in the range characteristic of C type RNA retroviruses, with associated DNA polymerase activity. Fresh tumor cells obtained from six children with astrocytoma and seven children with medulloblastoma, together with one sample of normal brain tissue and normal leukocytes from brain tumor patients were assayed by several characteristics for the presence of primate retrovirus. One of six (17%) astrocytomas and four of seven (57%) medulloblastomas released RNA particles which banded in sucrose gradients at a density of 1.16-1.18 g/cm3 together with a short segment of DNA, which was eliminated by prior ribonuclease treatment and two proteins of 28k and 16k daltons. These findings were compatible with the presence of a primate retrovirus. Immune coprecipitation of 125I-labeled proteins from the 1.16-1.18 g/cm3 gradient region failed to show any reactivity with antisera to p28 core antigens or the p70 reverse transcriptase antigens of simian sarcoma virus, baboon endogenous virus or Mason Pfizer virus. Assays for DNA polymerase activity in culture supernatant fluid showed only a low amount of activity with template preference not characteristic of the retroviral reverse transcriptase enzyme. (Author abstract) (21 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

7. EPSTEIN-BARR VIRUS INCREASES THE PROLIFERATIVE RESPONSE AND THE GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTIONS IN AUTOLOGOUS MIXED LYMPHOCYTE REACTION.

Palacios R

Dept. Immunobiology, Wallenberg Lab., Karolinska Inst., S-104 05 Stockholm, Sweden

Scand J Immunol; 15(1):17-24 1982

Epstein-Barr virus (EBV) infection of stimulator cells significantly increased the proliferative response of T cells in the autologous mixed lymphocyte reaction (AMLR). The addition of a monoclonal anti-HLA-DR antibody to AMLR cultures in which either EBV-infected or non-infected non-T cells were used as stimulator cells strongly inhibited the proliferative response irrespective of the presence of EBV. It is concluded that EBV does not by itself activate the responding cells and that HLA-DR antigens are necessary to trigger T cells. Increased generation of suppressor T cells, determined in both alloantigen-induced DNA synthesis and pokeweed-mitogen-stimulated immunoglobulin production, was found after an EBV infection of stimulator cells. Similarly, EBV-infected non-T cells significantly increased the generation of killer T cells, determined in three different types of target cells: phytohemagglutinin-stimulated mononuclear cells, EBV-transformed cells, and concanavalin-A-activated murine spleen cells. The increased T-cell responses after an EBV infection may reflect the attempts in vivo to control and hold in check the viral infection. (Author abstract) (33 Refs)

8. ESTABLISHMENT AND CHARACTERIZATION OF SV40-TRANSFORMED HUMAN BREAST EPITHELIAL CELL LINES.

Chang SE, Keen J, Lane EB, Taylor-Papadimitriou J

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

Cancer Res; 42(5):2040-2053 1982

Human breast epithelial cells cultured from milk have been transformed with SV40. Indirect immunofluorescence tests using monoclonal antibodies show that cells from clones grown in soft agar have SV40 large T-antigen in their nuclei and epithelia-specific tonofilament antigens on their intermediate filaments. In primary cultures of milk epithelial cells, the tonofilaments form a characteristic delicate basketwork throughout the cytoplasm, but in the SV40-transformed epithelial cell strains, the filament network is grossly distorted. Insulin, hydrocortisone, and serum stimulate the growth of the cell strains. At passages 8 to 11, the cell strains become quiescent and usually die. One cell strain survived this crisis period and gave rise to the fR series of cell lines. Most cell lines have a cuboidal morphology and react with a monoclonal antibody that recognizes a differentiation antigen on the membranes of breast epithelia. Line fR2 expressed the highest level of this antigen whereas fR5, the only fR line isolated with fusiform morphology, had relatively little. The in vitro-transformed lines may be related to the two dominant epithelial cell types seen in primary milk cultures and could be useful for studying the relationship between transformation and differentiation in human mammary epithelial cells. (Author abstract) (36 Refs)

9. CHANGES IN PROSTAGLANDIN LEVELS IN CULTURES OF SV40-TRANSFORMED MACROPHAGE CELL LINES IN RELATION TO THEIR PHENOTYPIC EXPRESSION.

Tanigawa T, Suzuki T, Takayama H, Takagi A

Dept. Bacteriology, Tottori Univ. Sch. Medicine, Yonago, Tottori 683, Japan

Microbiol Immunol; 26(1):59-66 1982

Prostaglandin (PRG) levels were determined in culture fluids of simian virus 40-transformed cells, line 28-12 and its subline, and the release of PRG by the cells when they are treated with lipopolysaccharide (LPS) and OK-432 (a streptococcal preparation from penicillin-attenuated Streptococcus pyogenes) was investigated. Low levels of PRG were detected in Dulbecco's modified Eagle's medium, and significantly higher levels (4,921 +-140 picog/ml) were detected in heat-inactivated fetal calf serum. 28-12 cells were cultivated for 16 days and the medium was changed every 4 days. A low level of PRG was detected in 4-day culture medium during the growing phase of the cells. When the proportion of phagocytic cells increased during the stationary phase, a decrease in PRG levels was observed. The levels of PRG remained lower than background levels and constant during the culture period when the 28-12 subline isolated by cultivation with cytosine arabinoside (28-12Ara) was cultivated without a change in the medium for 4 days. Non-phagocytic 28-12 cells and phagocytic 28-12Ara cells were cultivated for 24 hr in the presence and absence of LPS (1 ug/ml) and OK-432 (25 ug/ml). The release of PRG by 28-12Ara cells was markedly enhanced, whereas its release by 28-12 cells was not affected. The results indicate the correlation between the phenotypic change from the nonphagocytic to the phagocytic state and a decrease in PRG levels in culture fluids, and that phagocytic cells are responsive to PRG inducers, whereas nonphagocytic cells are not. (27 Refs)

10. ENHANCED TRANSFORMATION OF HUMAN FIBROBLASTS BY ORIGIN-DEFECTIVE SIMIAN VIRUS 40.

Small MB, Gluzman Y, Ozer HL

Dept. Biological Sciences, Hunter Coll., City Univ. New York, New York, NY, 10021

Nature; 296(5858):671-672 1982

Wild-type simian virus 40 (SV40) exhibits a low efficiency in transforming semipermissive human fibroblasts (HF). To investigate whether the low efficiency of transformation is related to the ability of SV40 DNA to replicate autonomously in HF, an SV40 mutant defective in the origin of DNA replication (SV ori-) was utilized. A comparison of intact superhelical form I SV40, form I plasmid SV ori+, form I plasmid SV ori-, linear form III plasmid SV ori+, and form III plasmid SV ori- showed that SV ori- DNA was the most efficient in transforming HF as assayed by focus formation in monolayer and colony formation in agarose (anchorage independence). To test the possibility that the enhanced transforming efficiency of SV ori- might be due to the presence of adjoining plasmid sequences and/or modification of DNA through propagation in a bacterial host, the efficiency of transformation by linearized (form III) virion DNA was compared with linear DNAs from SV ori+ and SV ori-, from which plasmid DNA was removed. Again SV ori- was most efficient. However, residual contribution from the bacterial environment (eg methylation) is likely because form III SV ori+ transforms more efficiently than form III SV40. The possibility of secondary infection being responsible for the reduced transforming ability of viral DNA was tested by using DNA from which a late region portion of the genome had been removed, precluding formation of viral particles. In this case, no improvement in transforming ability was observed. These results demonstrate that the efficiency of transformation of semipermissive HF can be enhanced by using a viral DNA defective at the origin of replication. Plasmid SV ori- appears to be a vector of choice for SV40 transformation of human fibroblasts. (22 Refs)

11. FUNCTION OF ADENOVIRUS TERMINAL PROTEIN IN THE INITIATION OF DNA REPLICATION.

Tamanoi F, Stillman BW
Cold Spring Harbor Lab., P. O. Box 100, Cold Spring Harbor, NY, 11724
Proc Natl Acad Sci USA; 79(7):2221-2225 1982

An early event in the initiation of adenovirus DNA replication is the formation of a covalent complex between the 87,000-dalton adenovirus terminal protein precursor and 5'-dCMP (pTP-dCMP complex). Nuclear extracts prepared from adenovirus-infected HeLa cells catalyzed complex formation in the presence of ATP, Mg++, and adenovirus DNA-protein complex but were not active when Pronase-treated DNA was used as template. The activity has been partially purified by chromatography on denatured DNA-cellulose and used to examine whether the 55,000-dalton terminal protein on adenovirus DNA is required for pTP-dCMP complex formation. Results obtained with either DNA-protein complex or Pronase-treated DNA were identical to those obtained using crude nuclear extracts. However, after treatment with piperidine to remove residual peptides, Pronase-treated DNA supported complex formation with the partially purified activity but not with crude extracts. In addition, when a plasmid containing an origin of adenovirus DNA replication was used as template, the pTP-dCMP complex was formed provided the plasmid was linearized in such a way that the origin was located at the end of the molecule. Neither linearized plasmid DNA with an internal origin nor supercoiled plasmid DNA supported complex formation. Furthermore, after heat denaturation, the linear plasmid DNA still supported complex formation, again provided that the origin was located at the end of the molecule. The partially purified protein fraction supported a limited amount of DNA chain elongation, which permitted exact positioning of the initiation site. These results suggest that enzymes responsible for complex formation recognize a DNA sequence at the origin and that the terminal protein on the template DNA plays a subordinate role. (Author abstract) (22 Refs)

VIRUS REPLICATION AND EXPRESSION

12. METHYLATION OF THE VIRAL GENOME IN AN IN VITRO MODEL OF HERPES SIMPLEX VIRUS LATENCY.

Youssoufian H, Hammer SM, Hirsch MS, Mulder C
Dept. Pharmacology, Molecular Genetics and Microbiology, Univ. Massachusetts Medical Sch., Worcester, MA, 01605
Proc Natl Acad Sci USA; 79(7):2207-2210 1982

An in vitro model of latency of herpes simplex virus type 1 (HSV-1) in a lymphoid cell line has been developed recently. CEM cells persistently infected with HSV-1 transiently ceased to produce virus for 24 days. This nonproductive state could either be reversed with phytohemagglutinin or maintained with concanavalin A. This system was used to study the relationship between DNA methylation and HSV-1 latency. DNA was probed for methylation by comparing the cleavage patterns generated by two pairs of restriction endonucleases (Sma I vs Xma I and Hpa II vs Msp I); these enzymes show differential activity reflecting methylation of the recognition sequences. Viral DNA in the concanavalin A-treated cells (not producing virus) was found to be extensively methylated. By contrast, no methylated copies were detected in viral DNA from producer cells. About 800 days after the initial infection, the productive culture once again became nonproductive. Viral sequences in the latter cells were also methylated. Reconstitution experiments revealed 1-2 copies of viral DNA in cells from the latent stages and 40-80 copies in cells from productive stages. Most (if not all) of the viral genome is present in cells from various productive and latent stages. No differences in sequence arrangement were detected (although a terminal fragment of intracellular HSV-1 DNA appeared to be under-represented in latent cells). These results suggest a role for DNA methylation in the mechanism of HSV-1 latency in this system. (Author abstract) (23 Refs)

13. SITE-SPECIFIC CLEAVAGE/PACKAGING OF HERPES SIMPLES VIRUS DNA AND THE SELECTIVE MATURATION OF NUCLEOCAPSIDS CONTAINING FULL-LENGTH VIRAL DNA.

Vlazny DA, Kwong A, Frenkel N
(c/o Frenkel) Dept. Biology, Univ. Chicago, Chicago, IL, 60637
Proc Natl Acad Sci USA; 79(5):1423-1427 1982

Defective genomes present in serially passaged herpes simplex virus (HSV) stocks have been shown to consist of tandemly arranged repeat units containing limited sets of the standard virus DNA sequences. Invariably, the HSV defective genomes terminate with the right (S component) terminus of HSV DNA. Because the oligomeric forms can arise from a single repeat unit, it has been concluded that the defective genomes arise by a rolling circle mechanism of replication. We now report on our studies of defective genomes packaged in viral capsids accumulating in the nuclei and in mature virions (enveloped capsids) trans-located into the cytoplasm of cells infected with serially passaged virus. These studies have revealed that, upon electrophoresis in agarose gels, the defective genomes prepared from cytoplasmic virions comigrated with nondefective standard virus DNA (Mr 100 x 10(6)). In contrast, DNA prepared from capsids accumulating in nuclei consisted of both full-length defective virus DNA molecules and smaller DNA molecules of discrete sizes, ranging in Mr from 5.5 to 100 x 10(6). These smaller DNA species were shown to consist of different integral numbers (from 1 to approximately 18) of defective genome repeat units and to terminate with sequences corresponding to the right terminal sequences of HSV DNA. We conclude on the basis of these studies that (i) sequences from the right end of standard virus DNA contain a recognition signal for the cleavage and packaging of concatemeric viral DNA, (ii) the sequence-specific cleavage is either a prerequisite for or occurs during the entry of viral DNA into capsid structures, and (iii) DNA molecules significantly shorter than full-length standard viral DNA can become encapsidated within nuclear capsids provided they contain the cleavage/packaging signal. However, capsids containing DNA molecules significantly shorter than standard virus DNA are not translocated into the cytoplasm. (Author abstract) (31 Refs)

14. COMPARISON OF THYMIDINE KINASE ACTIVITIES INDUCED IN CELLS PRODUCTIVELY INFECTED WITH HERPESVIRUS SAIMIRI AND HERPES SIMPLEX VIRUS.

Honess RW, O'Hare P, Young D
Div. Virology, Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
J Gen Virol; 58(part2):237-249 1982

The replication of unselected strains of herpesvirus saimiri (HVS) was sensitive to bromodeoxyuridine and bromovinyldeoxyuridine (BVdU) but insensitive to acycloguanosine (ACG), in contrast to the growth of herpes simplex virus (HSV) which was sensitive to all three analogues. Mutants of HVS resistant to bromodeoxyuridine and BVdU could be selected by growth in the presence of these inhibitors. Productive infections of owl monkey kidney or Vero cell cultures by unselected strains of HVS resulted in increases in a thymidine kinase (TK) activity which was deficient in cells infected with bromodeoxyuridine-resistant mutants of the virus. Induction of the virus enzyme promoted a net increase in the uptake and incorporation of exogenous labeled thymidine in the face of the progressive inhibition of the overall incorporation of [35S]methionine and [3H]uridine into productively infected cells. The TK induced in cells infected with HVS differed from the major activity of uninfected cells and resembled that encoded by HSV in its capacity to phosphorylate iododeoxyuridine and in the sensitivity of all the thymidine phosphorylating activity to competition by BVdU. However, in contrast to the HSV Tk, which phosphorylated deoxycytidine and iododeoxycytidine relatively efficiently and was sensitive to ACG, the HVS enzyme did not phosphorylate deoxycytidine or iododeoxycytidine and was insensitive to ACG. Whilst HVS, therefore, shares the characteristic of other members of the herpesvirus group of inducing a novel TK, the properties of the HVS-induced enzyme differ significantly from the enzyme of the prototype herpesvirus, HSV. The properties of the HVS TK are nonetheless sufficiently distinct from those of the uninfected cell to provide a possible basis for selective antiviral chemotherapy based on preferential phosphorylation of nucleoside analogues such as BVdU by infected cells. (Author abstract) (40 Refs)

15. EVIDENCE AGAINST INVOLVEMENT OF HOST TRANSCRIPTION IN THE REPLICATION OF VACCINIA AND HERPES SIMPLEX VIRUSES.

Silver M, Dales S
(c/o Dales) Cytotobiology Group, Dept. Microbiology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Virology; 118(1):214-218 1982

Vaccinia and herpes simplex viruses are unable to multiply in cells treated with the toxin alpha-amanitin, which specifically blocks host transcription involving RNA polymerase II (pol II). However, these agents are replicated in host cells made nonfunctional by intense gamma irradiation when RNA synthesis, including poly(A)-containing RNA and induction of biological functions, exemplified by the antiviral state, are inhibited. From this and previous evidence it is concluded that requirement for pol II or subunit(s) thereof by pox- and herpesviruses is probably related to transcription from the viral, not the host genome. (Author abstract) (11 Refs)

16. ULTRASTRUCTURAL STUDIES ON THE REPLICATION OF HERPES SIMPLEX VIRUS IN PK AND XTC-2 CELLS.

Ciampor F, Szanto J
Inst. Virology, Slovak Acad. Sciences, 809 39 Bratislava, Czechoslovakia
Acta Virol (Praha); 26(1/2):67-72 1982

Ultrastructural changes showed the following characteristics of restricted replication of herpes simplex virus 1 (HSV 1) strains MA and HSZP in PK and XTC-2 cells: (1) minimal cytopathic changes in PK cells as compared to more pronounced alterations in XTC-2 cells; (2) formation of single nucleocapsids or their absence in the nuclei of PK cells infected with the HSZP strain; (3) lack of budding and envelopment and absence of reduplication of the nuclear membrane; (4) persistence of partially uncoated virions within the endocytic vacuoles in the cytoplasm of PK cells; and (5) formation of dense inclusion bodies in addition to the presence of defective virions in the cytoplasm of XTC-2 cells and vacuolation of their cytoplasmic membranes. The replication of HsV 1 in PK and XTC-2 cells seemed to be blocked at both early and late stages of virus replication. At low multiplicity of infection, no virus particles were formed. (Author abstract) (14 Refs)

17. WHAT DO B LYMPHOCYTES AND NASOPHARYNGEAL EPITHELIUM HAVE IN COMMON?

North JR
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Immunol Today; 2(12):232-233 1981

The mechanism of Epstein-Barr virus (EBV) entry into nasopharyngeal epithelial cells is unknown. Evidence is presented demonstrating that of the cell types known to support expression of the EBV genome, only human and marmoset B lymphocytes and a squamous epithelial cell subset residing in the human nasopharynx are immortalized and express Epstein-Barr nuclear antigen. The common denominator between the cell types remains to be determined. (11 Refs)

18. PRESENCE OF THE PRE-MRNA FOR THE 72K DNA BINDING PROTEIN IN HNRNP FROM EARLY ADENOVIRUS-2 INFECTED HELA CELLS.

Kucherer C, Marty L, Blanchard J
Laboratoire de Biologie Moleculaire, Universite des Sciences et Techniques du Languedoc, Place E. Bataillon, 34060 Montpellier Cedex, France
Biochem Biophys Res Commun; 105(2):603-609 1982

An investigation was made on the RNa transcribed from adenovirus-2 (Ad-2) early region E2, which codes for the 72,000 dalton DNA binding protein (72K DBP). Tritium-labeled ribonucleoprotein particles (RNP) prepared from Ad-2 infected HeLa cells were deproteinized and the labeled RNA was hybridized to the EcoRI B DNA restriction fragment bound to a nitrocellulose filter. This DNA fragment carries the 3' half of the 72K DBP gene. EcoRI B specific RNA from nuclear RNP (hnRNP) was found in structures sedimenting in a sucrose gradient between 70 and 200S, while EcoRI B specific RNA from cytoplasmic RNA was found in a narrow distribution around 50S. Polyacrylamide gel electrophoresis of the RNA from the early Ad-2 transcripts showed a single 18S species in the cytoplasmic RNP in contrast to nuclear RNP, which showed a heterodisperse distribution of RNa in the 28S to 10S range. Previous studies indicate three size classes of nuclear RNA transcribed from the early region E2: a 28S pre-mRNA which is the first polyadenylated species likely to occur by cleavage of the primary transcript and which contains two intervening sequences, a 23S intermediate RNA and a 20S mature mRNA. These data indicate that, except for the species smaller than 18S which are degradation products, the newly synthesized intact transcripts of the gene coding for Ad-2 72K DBP are present in large hnRNP. Northern blot hybridization of RNA from early Ad-2 transcripts to EcoRI B DNA revealed that the EcoRI B probe hybridized to two components which correspond to the unspliced 28S pre-mRNA and to the mature 18S mRNA; the 23S transitory species was not observed. This demonstrates, in addition to the unspliced 28S pre-mRNA, the existence of mature mRNA molecules in nuclear RNP which differ in sedimentation coefficient from cytoplasmic mRNP. (30 Refs)

19. STUDIES ON PROTEINS OF SIMIAN SARCOMA-ASSOCIATED VIRUS WITH DIFFERENT GROWTH HISTORY.

Warnaar SO, Huiskens-Van Der Meij C, Kool-Kofoed L, Mooren HW

Lab. Pathology, State Univ. Leiden, Wassenaarseweg 62, 2333 AL Leiden, The Netherlands

J Gen Virol; 59(part1):65-71 1982

Simian sarcoma-associated virus (SSaV) was repeatedly passaged on three human cell lines. The proteins of the progeny virus were analyzed for the presence of variant polypeptides. Occasionally, a few variant polypeptides were observed. One-dimensional peptide maps of the major virus protein p30 revealed no modifications after 25 cycles of infection on the three cell lines studied. The peptide map of Pr65gag of virus grown through 25 passages on a human chondrosarcoma cell line was slightly different from that of the virus stock before passaging. The relative amount of the virus protein p30 as compared to p18 and p16 (possibly the SSaV equivalents of p15E and p12E) was variable depending on the host cell. Virus grown on Daudi cells was relatively deficient in p18 and p16. These virus particles were morphologically altered and had a low infectivity. (Author abstract) (18 Refs)

20. SIMIAN FOAMY VIRUS PSEUDOTYPES OF VESICULAR STOMATITIS VIRUS: PRODUCTION AND USE IN SERO-EPIDEMIOLOGICAL INVESTIGATIONS.

Schnitzer TJ

Rackham Arthritis Res. Unit, Univ. Michigan Medical Sch., Ann Arbor, MI, 48109

J Gen Virol; 59(part1):203-206 1982

Simian foamy virus (SFV) pseudotypes of vesicular stomatitis virus have been successfully produced and their host range characterized. The availability of these pseudotypes has permitted the development of a rapid, quantitative assay to measure neutralizing antibody titers to SFV that has proved useful in a sero-epidemiological study. (Author abstract) (8 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

21. RETROVIRUS LONG TERMINAL REPEATS ACTIVATE EXPRESSION OF CODING SEQUENCES FOR THE HERPES SIMPLEX VIRUS THYMIDINE KINASE GENE.

Joyner A, Yamamoto Y, Bernstein A

Ontario Cancer Inst., Univ. Toronto, 500 Sherbourne St., Toronto, Ontario, M4X 1K9, Canada

Proc Natl Acad Sci USA; 79(5):1573-1577 1982

In this study, we demonstrate that the long terminal repeats (LTRs) of a murine retrovirus can activate expression of heterologous gene coding sequences from which a functional promoter region has been deleted. Recombinant plasmid clones were obtained that contained both cloned fragments of Friend spleen focus-forming virus (SFFV) DNA and the herpes simplex virus (HSV) thymidine kinase (TK; ATP:thymidine 5'-phosphotransferase, EC 2.7.1.21) gene (tk). The effects of the LTR on tk expression were determined by constructing clones containing tk coding sequences with or without 5' sequences necessary for the initiation of transcription, inserted either 200 or 1,200 base pairs downstream from the SFFV 5' LTR. The expression of the HSV TK protein by these clones was tested by gene transfer of the clones into TK- mouse cells and assay of TK enzyme activity in TK+ transformants. These experiments demonstrate that: (i) the SFFV 5' LTR activates expression of tk coding sequences when these sequences are inserted 200 base pairs downstream from, and in the same orientation as, the LTR; (ii) tk is not activated when placed 1,200 base pairs downstream from, and in the same orientation as, the LTR or when tk is inserted in either site in the opposite orientation as the LTR; (iii) the SFFV 5' LTR does not interfere with in vivo expression of tk when it is flanked by homologous 5' promoter sequences. The implication of these observations for retrovirus oncogenesis and animal cell genetics is discussed. (Author abstract) (40 Refs)

22. ISOLATION AND PRELIMINARY CHARACTERIZATION OF A PHOSPHONOACETIC ACID-RESISTANT AND TEMPERATURE-SENSITIVE MUTANT OF HERPES SIMPLEX VIRUS TYPE I.

Daksis JI, Priemer MM, Chan VL

Dept. Microbiology and Parasitology, Univ. Toronto, Toronto, Ontario M5S 1A1, Canada

J Virol; 42(1):20-29 1982

A group of 43 phosphonoacetic acid (PAA)-resistant mutants of herpes simplex virus Type 1 was isolated after the mutagenesis of infected cells with nitrosoguanidine. One of these mutants, designated PAA1rts1, was found to be temperature sensitive (ts), that is, unable to replicate at 39.5 C, the nonpermissive temperature. Recombination analysis of PAA1rts1 indicated that the PAA1r mutation and the ts1 mutation are loosely linked and are located on two separate genes. PAA1rts1 showed a defect in viral DNA synthesis at 39.5 C, which presumably can be attributed to the production of a PAA-resistant and thermolabile DNA polymerase. PAA1rts1 was also defective in the shutoff of host DNA synthesis at the restrictive temperature. (Author abstract) (20 Refs)

23. USE OF RECOMBINANT PLASMIDS TO INVESTIGATE THE STRUCTURE OF THE HUMAN CYTOMEGALOVIRUS GENOME.

Oram JD, Downing RG, Akrigg A, Dollery AA, Duggleby CJ, Wilkinson GW, Greenaway PJ
Genetic Manipulation Lab., PHLS Centre for Applied Microbiology and Res., Porton Down, Salisbury, Wiltshire, SP4 OJG, England
J Gen Virol; 59(part1):111-129 1982

Human cytomegalovirus (HCMV) DNA was digested with restriction endonucleases and the fragments characterized with respect to mol wt and relative mole proportions. The terminal fragments were identified by digesting HCMV DNA with exonucleases before restriction endonuclease treatment and subsequent gel analysis. The HindIII fragments of HCMV DNA were cloned in Escherichia coli and recombinant plasmids were characterized by digestion with restriction endonucleases and by molecular hybridization with HindIII, BglII and XbaI fragments of the virus genome. Data from these experiments were used to construct physical maps of HCMV DNA for the HindIII, BglII and XbaI restriction endonucleases. The terminal regions of the genome and the region containing fragment HindIII M were shown to be heterogenous. (Author abstract) (20 Refs)

24. TRANSCRIPTION OF ADENOVIRUS CORES IN VITRO: MAJOR RNA PRODUCTS DIFFER FROM THOSE MADE FROM A DNA TEMPLATE.

Daniell E, Fedor MJ
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Proc Natl Acad Sci USA; 79(6,part1):1834-1838 1982

Intact cores of adenovirus type 5 were transcribed in vitro in extracts derived from uninfected HeLa cells, and the products were analyzed by hybridization to restricted viral DNA. Predominant transcripts from cores were distinctly different from transcripts generated from deproteinized DNA. The extracts contained RNA polymerase II and RNA polymerase III. Transcription from cores was completely inhibited by low levels of alpha-amanitin, and there was little or no hybridization of products to the region of the genome encoding the small polymerase III-dependent virus-associated RNA that was major transcript from the DNA template. The major transcripts from cores hybridized to the rightward-transcribed strand of the region between 75 and 89 map units, early region 3 of the adenovirus genome. There was several-fold more transcription of this region in cores than of the region downstream from the major late promoter, which predominates among polymerase II transcripts from DNA. (Author abstract) (38 Refs)

25. IDENTIFICATION AND PURIFICATION OF A PROTEIN ENCODED BY THE HUMAN ADENOVIRUS TYPE 2 TRANSFORMING REGION.

Green M, Brackmann KH, Cartas MA, Matsuo T
Inst. Molecular Virology, St. Louis Univ. Medical Center, St. Louis, MO, 63110
J Virol; 42(1):30-41 1982

The human adenovirus Type 2 (Ad2) transforming genes are located in early regions E1a (map position 1.3 to 4.5) and E1b (map position 4.6 to 11.2). We have identified and purified to near homogeneity a major 20,000-mol-wt (20K) protein and have shown that it is coded by E1b. Using an Ad2-transformed cell antiserum which contained antibody to E1b-coded proteins, we immunoprecipitated 53K and 19K proteins from the nucleoplasm and 53K, 19K, and 20K proteins from the cytoplasmic S-100 fraction of Ad2 productively infected and Ad2-transformed cells. The 19K protein was present in both the nucleoplasm and the cytoplasm, where the 20K protein was found only in the cytoplasm. The 53K and 19K proteins are known Ad2 E1b-coded proteins. The 20K protein was purified to near homogeneity in 20 to 50% yields by sequential DEAE-Sephacel chromatography and reverse-phase high-performance liquid chromatography. Purified 20K protein shares most of its methionine-labeled tryptic peptides with E1b-53K, as shown by reverse-phase high-performance liquid chromatography, and therefore is closely related to the 53K protein. The 19K protein does not appear to share tryptic peptides with either 20K or 53K protein. To provide more direct evidence that 20K protein is virus-coded we translated E1b-specific mRNA in vitro. Both immunoprecipitation analysis and high-performance liquid chromatography purification of the translated product identified a 20K protein that has the same tryptic peptides as the 20K protein isolated from infected and from transformed cells. These findings suggest that the Ad2 20K protein is a primary translation product of an Ad2 E1b mRNA. (Author abstract) (39 Refs)

26. CLONING OF ADENO-ASSOCIATED VIRUS INTO PBR322: RESCUE OF INTACT VIRUS FROM THE RECOMBINANT PLASMID IN HUMAN CELLS.

Samulski RJ, Berns KI, Tan M, Muzyczka N
Dept. Immunology and Medical Microbiology, Univ. Florida Coll. Medicine, Gainesville, FL, 32610
Proc Natl Acad Sci USA; 79(6,part1):2077-2081 1982

We have cloned intact duplex adeno-associated virus (AAV) DNA into the bacterial plasmid pBR322. The AAV genome could be rescued from the recombinant plasmid by transfection of the plasmid DNA into human cells with adenovirus 5 as helper. The efficiency of rescue from the plasmid was sufficiently high to produce yields of AAV DNA comparable to those observed after transfection with equal amounts of purified virion DNA. Thus, the recombinant plasmid itself may be a model for studying the rescue of a latent AAV viral infection. In addition, the efficient rescue of viable AAV from the recombinant plasmid should facilitate the genetic analysis of AAV. Finally, the results of an analysis of the DNA from rescued virions indicate that an inversion of the AAV terminal sequences occurred during replication. (Author abstract) (19 Refs)

27. SEQUENCE HOMOLOGY BETWEEN AVIAN AND HUMAN ADENOVIRUSES.

Alestrom P, Stenlund A, Li P, Bellett A, Pettersson U
(c/o Pettersson) Dept. Microbiology, Univ. Uppsala, The Biomedical Center, S-751 23 Uppsala, Sweden
J Virol; 42(1):306-310 1982

Studies of hybridization between fowl adenovirus Type 1 (chicken embryo lethal orphan virus) DNA and human adenovirus Type 2 DNA revealed two short but distinct regions which cross-hybridized under stringent conditions. One of the homologous regions was located between map positions 18.1 and 19.3 and did not correspond to any gene recognized so far. The second region mapped in the hexon gene between positions 57 and 58. (Author abstract) (19 Refs)

28. TRANSCRIPTION AND ACCURATE POLYADENYLATION IN VITRO OF RNA FROM THE MAJOR LATE ADENOVIRUS 2 TRANSCRIPTION UNIT.

Chen-Kiang S, Wolgemuth DJ, Hsu MT, Darnell JE
Memorial Sloan Kettering Cancer Center, New York, NY, 10021
Cell; 28(3):575-584 1982

Nucleoprotein complexes with in vitro transcription activity were isolated from HeLa cells late in lytic infection with Adenovirus type 2 (Ad2). Both polymerase II and polymerase III were active in these extracts, and greater than 85% of the labeled RNA was Ad2-specific. Electrophoretic analyses and Southern blot analyses demonstrated that RNA complementary to the entire 30 kb late transcription unit including RNA near the presumed termination site was synthesized. The addition of DRB (5,6,dichloro-1-beta-D-ribofuranosyl-benzimidazole) in vivo prior to the isolation of the complexes resulted in accumulation of polymerase II at the promoter proximal sites, but nascent chains started in vivo in DRB were successfully elongated in vitro. Approx 10% of the RNA labeled in vitro contained poly(A), and the length of poly(A) was very similar to that of nuclear RNA isolated from Ad2-infected cells. The in vitro sites of poly(A) addition were specific-labeled poly(A)-terminated RNA molecules ended at a point on the genome coincident with previously mapped poly(A) sites of mRNAs produced in vivo. In addition, the polyadenylation enzyme (or enzymes) cosediment with the nucleo-protein complexes during sucrose gradient centrifugation since gradient purified complexes synthesize poly(A) containing RNA in vitro in the absence of any added nuclear extract. (Author abstract) (63 Refs)

29. SIMIAN VIRUS 40-RABBIT BETA-GLOBIN RECOMBINANTS LACKING LATE MRNA SPLICE SITES EXPRESS CYTOPLASMIC RNAS WITH ALTERED STRUCTURES.

White RT, Berg P, Villarreal LP
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
J Virol; 42(1):262-274 1982

Deletions were introduced at exon-intron boundaries in the late region of a simian virus 40-beta-globin cDNA recombinant to study the role of splicing in the formation of simian virus 40 late cytoplasmic RNAs. The recombinant was used as a wild type because it allowed characterization of mutant RNAs expressed from defective genomes in the presence of comparable RNAs contributed by the coinfecting helper virus. Removal of a 17-base pair segment at map position 0.76, which included a portion of the leader sequence implicated in the splicing of the major 16S mRNA, prevented expression of 16S-type mRNA. The same mutant accumulated cytoplasmic 19S-type mRNA, but the assortment of the 5' ends of these mRNAs differed from the assortment in the wild-type counterparts. Another mutant that lacks nucleotide sequences implicated in the splicing of the major 16S mRNA and one of the principal 19S-type RNAs accumulated a 16S-type mRNA with a previously undetected leader splice, an assortment of 19S mRNAs with new or normally underrepresented splices, and even a species of unspliced cytoplasmic 19S mRNA. (Author abstract) (36 Refs)

30. CONSTRUCTION AND CHARACTERIZATION OF SV40 RECOMBINANTS WITH BETA-GLOBIN CDNA SUBSTITUTIONS IN THEIR EARLY REGIONS.

Southern PJ, Howard BH, Berg P
(c/o Berg) Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA, 94305
J Mol Appl Genet; 1(3):177-190 1981

A complementary DNA (cDNA) segment coding for rabbit beta-globin (RBG) was inserted at three different sites in the early region of simian virus 40 (SV40). Monkey kidney cells infected with each hybrid SV40 genome produced stable, spliced polyadenylated messenger RNA (mRNA) containing the RBG cDNA sequence. Only the hybrid mRNAs containing the RBG coding sequences immediately proximal to the 5' end of the mRNA underwent translation to produce RBG. The recombinants containing the RBG coding sequence towards the 3' end of the early region yielded small t antigen and abbreviated forms of large T antigen, but little or no detectable RBG. The results suggested that the position of the RBG cDNA segment in the early region of SV40 influences the translation of the transduced coding sequences. (41 Refs)

31. SYSTEMATIC ALTERATION OF THE NUCLEOTIDE SEQUENCE PRECEDING THE TRANSLATION INITIATION CODON AND THE EFFECTS ON BACTERIAL EXPRESSION OF THE CLONED SV40 SMALL-T ANTIGEN GENE.

Gheysen D, Iserentant D, Derom C, Fiers W
Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 17(1):55-63 1982

In a series of recombinant plasmids which contain the simian virus 40 small-t antigen gene under control of the thermoinducible pL promoter of phage lambda, a Shine-Dalgarno ribosome-recognition (SD) sequence was created at various distances in front of the small-t translation initiation codon. In some other constructions the distance between the initiating AUG and the SD sequence was conserved while the intervening nucleotides were changed. Effects of these variables on production levels of the 19,000-dalton full-size small-t protein and on the 14,500-dalton small-t-related species are explained in terms of messenger RNA secondary structure models that could be drawn for different plasmids. (19 Refs)

32. HIGH-LEVEL SYNTHESIS IN ESCHERICHIA COLI OF THE SV40 SMALL-T ANTIGEN UNDER CONTROL OF THE BACTERIOPHAGE LAMBDA PL PROMOTER.

Derom C, Gheysen D, Fiers W
Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 17(1):45-54 1982

A series of plasmids was constructed in which the small-t gene of simian virus 40 (SV40) is under transcriptional control of the leftward promoter (pL) of bacteriophage lambda. The trancscription is thermoinducible in a bacterial strain (Escherichia coli) which produces a temperature-sensitive repressor protein. Tryptic peptide analyses of the bacterial 14,500-and 19,000-dalton proteins and authentic small-t are presented. The 19,000-dalton protein was identified as a small-t antigen by specific precipitation with anti-T antiserum, coelectrophoresis on acrylamide gels with authentic small-t isolated from SV40-infected CV-1 cells, and by tryptic peptide analysis. (35 Refs)

33. MOLECULAR CLONING AND PARTIAL NUCLEOTIDE SEQUENCE OF HUMAN PAPILLOMAVIRUS TYPE 1A DNA.

Clad A, Gissmann L, Meier B, Freese UK, Schwarz E
(c/o Schwarz) Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Virology; 118(1):254-259 1982

Papilloma viruses contain a DNA genome of about 5 x 10(6). They belong in the papovavirus group and induce epithelial proliferation in a variety of animal species and in man. To date, eight types of papillomaviruses have been identified in different human papillomas, some of which show an increased tendency for malignant conversion. Due to the inability to propagate papillomaviruses in tissue culture, almost nothing is known about their genetic organization and gene expression. The use of recombinant DNA techniques now renders it possible to study in detail the molecular biology of papillomaviruses. Here we report the molecular cloning of the DNA of human papillomavirus Type 1a (HPV1a) in Escherichia coli using pBR 322 as vector and the nucleotide sequence of part of the HPV1a genome. The region of 1819 base pairs contains one of two pairs of short inverted repetitive sequences detected earlier by electron microscopic studies. Within the DNA sequence, three potential coding regions of only one orientation have been observed which allows prediction of the direction of transcription in this part of the HPV1a genome. (Author abstract) (22 Refs)

34. ISOLATION AND CHARACTERIZATION OF A HUMAN LOCUS HOMOLOGOUS TO THE TRANSFORMING GENE (V-FES) OF FELINE SARCOMA VIRUS.

Trus MD, Sodroski JG, Haseltine WA
Lab. Biochemical Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Biol Chem; 257(6):2730-2733 1982

A single locus (designated c-fes) in the human genome which exhibits homology to the transformation-specific onc gene (v-fes) of Snyder-Theilen feline sarcoma virus was identified by the Southern blot technique. Recombinant clones containing 16-to 18-kilobase inserts of human DNA including the c-fes locus were constructed. Restriction endonuclease mapping of these clones verified their identity with native human c-fes and demonstrated the presence of at least two sequences in human c-fes interrupting v-fes-homologous regions. The v-fes-homologous locus in the human genome spans about 4 kilobases. The 5'-3' orientation of the c-fes clones with respect to feline sarcoma virus proviral DNA was determined. The region of the human genome that is homologous to v-fes is proximal to the highly reiterated human Alu sequence but not to the highly reiterated human alphoid sequence. (Author abstract) (39 Refs)

35. HUMAN NUCLEOTIDE SEQUENCES RELATED TO THE TRANSFORMING GENE OF A MURINE SARCOMA VIRUS: STUDIES WITH CLONED VIRAL AND CELLULAR DNAS.

Chumakov IM, Zabarovsky ER, Prassolov VS, Mett VL, Kisselev LL
Inst. Molecular Biology, USSR Acad. Sciences, ul. Vavilova 32, Moscow V-334, USSR
Gene; 17(1):19-26 1982

Fragments of the human genome related to onc-gene of Moloney sarcoma virus (MSV), mos-specific, and Moloney leukemia virus (MLV)-specific nucleotide sequences were cloned. An attempt was made to visualize the expression of oncogenes by the Northern blotting technique, using a mos-specific probe, and preliminary data are presented. MSV clone 124 was isolated from tissue culture supernatant obtained from chronically infected TB cells. A total of 3 x 10(5) recombinant phages containing human DNA insert were subjected to screening. [32P]Complimentary (c)DNA-MSV was used as a probe and 30 labeled plaques were obtained. All of them were tested with the mos-specific probe, but with one exception, no mos-specific DNA was detected. After the whole screening procedure, 19 recombinant phages with inserts hybridizable with the mos-specific probe were selected. Clones isolated with various probes could be subdivided into those that contain MLV-related sequences and lack mos-related sequences and those that contain both types of sequences. The hybridization pattern of polyadenylic+RNA from normal mouse liver with [32P]cDNA-MSV is presented. Several fractions were revealed which hybridize also with cDNA-MLV. These RNA appeared to be transcripts of endogenous proretroviruses homologous to MLV which probably are present in mouse liver. When a mos-specific probe was used, no hybridization was detected with RNA isolated independently from several groups of mice. (32 Refs)

36. CHARACTERIZATION OF THE RIBONUCLEIC ACID OF A TYPE D RETROVIRUS (PMFV) ISOLATED FROM A PERMANENT HUMAN CELL LINE.

Mothes E
Zentralinstitut fur Krebsforschung, Lindenberger Weg, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(3):191-197 1982

Similarities in size, subunit structure, and the presence of associated RNA of the major RNA species of permanent human fibroblasts virus (PMFV), Mason-Pfizer monkey virus (MPMV), and other retroviruses were studied. The virus was propagated in suspension culture of human rhabdomyosarcoma A204 cells. PMFV 3H-RNA was extracted from purified virus (peak fraction 1.14-1.18 g/ml) by the phenol-phase method. Comparison of the profiles showed that PMFV contains high-(60-70 Svedberg units; S) and low-mol wt (approx 7 S) components. RNA was isolated with the same method from the 1.20-1.23 g/ml peak fraction (virus core). A high mol wt species (60-70 S) was observed. Treatment with heat (65 C) resulted in a decrease of the sedimentation coefficient to approx 30 S. Best results were obtained with RNA from fresh virus isolated from cell sediments. Chromatographic profiles obtained with 60-70 S PMFV 3H-RNA and with 30 S PMFV 3H-RNA from whole virions of virus core are shown. Radioactivity bound to the column eluted mainly at 30-45 C. This corresponded to polyadenylic acid (poly A) regions of 80-300 adenylate residues. The presence and length of the poly A stretch of PMFV RNA, the size of native 60-70 S PMFV RNA and its dissociation by heat to subunit structures of approx 30 S showed the similarity to MPMV RNA. (14 Refs)

IMMUNOLOGICAL STUDIES

37. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY TO HERPES SIMPLEX VIRUS-TRANSFORMED CELLS IN THE COURSE OF CERVICAL CARCINOMA.

Christenson B
Dept. Epidemiology, Natl. Bacteriological Lab., S-105 21 Stockholm, Sweden
Am J Epidemiol; 115(4):556-568 1982

The antibody-dependent cell-mediated cytotoxicity assay was used to determine whether humoral antibodies from women with cervical carcinoma in the presence of normal mononuclear cells could induce cytotoxicity to hamster embryo fibroblasts, originally transformed by herpes simplex virus Type 2 (HSV-2) (333-8-9), to a cervical carcinoma cell line (ME-180) and to a lung carcinoma cell line (A-549). Control groups consisted of 81 age-matched healthy women and 77 patients suffering from malignancies other than cervical carcinoma. Significant cytotoxicity to HSV-2-transformed cells was observed in sera from 20 of 28 (71%) surviving patients with cervical cancer who were followed with serum samples collected 6-24 mo after initial treatment. Comparison of serum samples obtained before initial treatment from 20 patients surviving the observation period of 60 mo or longer and from 20 patients who died during the observation period showed that the survivors had significantly higher cytolytic activity prior to treatment. Long-term survivors also showed a drop in cytolytic activity in sera obtained 30 mo or later after treatment. Patients with long survival but whose cancer finally caused death, had stronger cytolytic activity than those with short survival (24 mo or less). Patients with cervical cancer had significantly higher cytolytic activity to HSV-2-transformed cells and to the cervical carcinoma cells (ME-180) than age-matched control women and patients with malignancies other than cervical carcinoma. (Author abstract) (33 Refs)

38. A POPULATION STUDY OF HERPESVIRUS INFECTIONS AND HLA ANTIGENS.

Blackwelder WC, Dolin R, Mittal KK, McNamara PM, Payne FJ
Natl. Inst. Allergy and Infectious Diseases, NIH, Westwood Building, Room 739, Bethesda, MD, 20205
Am J Epidemiol; 115(4):569-576 1982

In a population-based study of herpesvirus infection and human leukocyte antigen (HLA) phenotype, conducted during the period 1977-1979 in the Framingham Study cohort, HLA-Bw16 was found less often and HLA-Cw2 more often in individuals with histories of herpes labialis than in other individuals. Similarly, both geometric mean antibody titer to herpes simplex Type 1 and proportion of individuals with detectable antibody were higher in those without Bw16 and in those with Cw2. No strong association was found between HLA and history of herpes zoster or titer to herpes simplex Type 2, varicella-zoster virus or cytomegalovirus. (Author abstract) (25 Refs)

39. THE INFLUENCE OF ANTIVIRAL SERUM ON CELLS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 1.

Karmysheva VYa, Rajcani J
Inst. Poliomyelitis and Viral Encephyalitides, USSR Acad. Medical Sciences, 142782 Moscow, USSR
Acta Virol (Praha); 26(1/2):79-85 1982

Homologous immune serum (IS) had an inhibitory effect on the accumulation of specific viral antigens in VERO cells infected with herpes simplex virus Type 1. When infected cells were incubated in the presence of IS, lower amounts of viral, both intracellular and membrane, antigens were found by quantitative immunofluorescence and immune cytolysis as compared to same infected cells incubated in the absence of IS. The possible mechanisms of this effect are discussed. (Author abstract) (15 Refs)

40. MORPHOLOGIC OBSERVATIONS OF CONTACT-INDUCED LYSIS OF EBV-INFECTED B LYMPHOCYTES BY AUTOLOGOUS HAND MIRROR T CELLS.

Thomas WJ, Duval-Arnould B, Creegan WJ, Schumacher HR, Forman DS, Strong DM
Clinical Investigation Center, Naval Regional Medical Center, San Diego, CA, 92134
Am J Hematol; 12(2):109-119 1982

To study the possible immunologic role of hand mirror lymphocytes (HML) in the control of Epstein-Barr virus (EBV)-infected B lymphocytes in patients with infectious mononucleosis (IM), we studied the in vitro interactions of these cells by time-lapse video light microscopy. Peripheral blood T lymphocytes isolated from three patients in the early recovery phase of IM were mixed with their autologous EBV-infected B cells. Motile lymphocytes with their characteristic hand mirror shape were observed to attach by their uropods to the B cells. The HML remained attached for variable periods ranging from 45-75 min. Following detachment, B cells that were in contact with HML underwent lysis. Mixtures of T cells from healthy donors and EBV-infected cell lines exhibited only rare uropod formation with no attachment or lysis of B cells. The present experiment indicates that contact-induced lysis of EBV-infected B lymphocytes is operative in IM and that this process is mediated by the HML. (Author abstract) (31 Refs)

41. MIGRATION INHIBITION CAUSED BY EBV-SPECIFIC 48K SUBCOMPONENT OF EBNA AND THE ASSOCIATED 53K CELLULAR PROTEIN.

Szigeti R, Luka J, Sternas L, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Int J Cancer; 29(4):413-416 1982

Leukocytes from EBV-seropositive but not seronegative healthy donors responded with significant migration inhibition to the 48K subcomponent of the Epstein-Barr virus determined nuclear antigen (EBNA), known to carry the virally determined antigenic specificity. A concentration of 10 ug/ml was still effective while 5 ug/ml had no detectable effect. EBNA-associated cellular 53K protein had no effect by itself, but it potentiated the effect of 48K, even if the latter was added at the subliminal concentration of 5 ug/ml. The related 53K protein, isolated from EBV-negative human lymphoma cells, was also effective, whereas the corresponding murine-tumor-associated 53K had no potentiating effect. Immunization of mice with an extract of DNA-binding proteins from EBV-carrying Raji cells, known to contain both 48K and 53K, induced a significant macrophage migration inhibition response, to both human 48K and 53K. Murine 53K was ineffective, however. Human but not murine 53K increased the migration inhibitory activity of subliminal concentrations of 48K in the murine macrophage system as well. These findings suggest that human but not murine 53K may reconstitute with 48K (EBNA) to form a highly immunogenic complex. (Author abstract) (24 Refs)

42. SERA FROM PATIENTS WITH UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA CONTAIN A FACTOR WHICH ABROGATES SPECIFIC EPSTEIN-BARR VIRUS ANTIGEN-INDUCED LYMPHOCYTE RESPONSE.

Sundar SK, Ablashi DV, Kamaraju LS, Levine PH, Faggioni A, Armstrong GR, Pearson GR, Krueger GR, Hewetson JF, Bertram G, Sesterhenn K, Menezes J

(c/o Menezes) Lab. Immunovirology, Pediatric Res. Center, St. Justine Hosp., 3175 Cote St. Catherine, Montreal (Quebec) H3T 1C5, Canada

Int J Cancer; 29(4):407-412 1982

A unique association of Epstein-Barr virus (EBV) with the undifferentiated nasopharyngeal carcinoma (NPC) is a well acknowledged phenomenon. We report here the detection of a factor present in the sera of NPC patients which inhibits the blastogenic response of lymphocytes from EBV seropositive individuals to EB virions or soluble antigens. This lymphocyte-stimulation inhibitor (LSI) was found to be associated with the IgA fraction of the serum immunoglobulins. No inhibitory activity was detected in the sera and their immunoglobulin fractions from healthy (both EBV-seropositive and seronegative) individuals and patients with other carcinomas of the head and neck region. Interestingly, the IgA-LSI was absent in the sera of NPC patients who were successfully treated and remained in remission, while it was readily detectable in the sera of NPC patients in relapse. LSI-positive IgA fractions did not inhibit mitogenic response of lymphocytes to phytohemagglutinin. Taken together, the data presented suggest that LSI is a specific inhibitor of the response of sensitized lymphocytes to EBV antigens and that it may indeed represent a marker of great clinical significance regarding undifferentiated nasopharyngeal carcinoma, particularly for its prognosis. (Author abstract) (36 Refs)

43. A MONOCLONAL ANTIBODY DEFINING A BURKITT LYMPHOMA ASSOCIATED ANTIGEN.

Wiels J, Fellous M, Lenoir G, Tursz T

Laboratoire de Immunologie, Clinique Institut G. Roussy, 94800 Villejuif, France

Protides Biol Fluid Proc Colloq; 29:899-902 1982

Reactivity of monoclonal antibody 38-13, obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma), was investigated. Negative results were obtained in all patients with B chronic lymphoid leukemia, acute lymphoid leukemia (T and nonT-nonB), acute myeloid leukemia, acute monoblastic leukemia, Hodgkin's disease, T cell lymphosarcoma, and B cell lymphosarcoma (nodular and diffuse). Positive results were observed in 4/8 patients with B cell Burkitt lymphoma. When the specific reactivity of 38.13 ascites was tested with a panel of cell lines of various origins, both by complement dependent lymphocytotoxicity tests and indirect membrane immunofluorescence assays, all the positive target cells were of Burkitt's lymphoma origin. Negative results were obtained with 15 Epstein-Barr virus positive lymphoblastoid cell lines, 4 T cell lines, a chronic myelogenous leukemia cell line, 4 teratoma cell lines, and one each of melanoma and neuroblastoma. The 38.13 monoclonal antibody may be useful for diagnosis and specific immunotherapy of Burkitt lymphomas. (8 Refs)

44. MONOCLONAL ANTIBODY AGAINST EBV-ASSOCIATED TRANSFORMATION ANTIGEN DETECTED IN VITRO AND IN VIVO.

Thorley-Lawson DA, Geilinger K, Schooley R

Div. Geographic Medicine, Tufts Univ. Sch. Medicine, Boston, MA, 02111

Protides Biol Fluid Proc Colloq; 29:739-742 1982

Transformation antigens on the surface of in vitro Epstein-Barr virus (EBV)-transformed B lymphocytes were defined by producing specific monoclonal antibodies. A hybridoma (17D6) was cloned and analyzed for its binding properties to a variety of EBV-positive and -negative B cell lines. The antibody reacted strongly with all of the EBV-positive lines and weakly with the EBV-negative lines. Similarly, a panel of EBV-negative cell lines from a variety of sources reacted only weakly with the 17D6 antibody. When a whole panel of EBV-infected cells from sources other than in vitro infection were tested, all the cell lines containing EBV were as positive as in vitro infected cells, including one cell line derived by spontaneous outgrowth from an EBV-positive individual and one from co-cultivation of normal lymphocytes from a seronegative individual with a nasopharyngeal carcinoma. Burkitt's lymphoma tumor cells reacted only weakly with the 17D6 antibody due to their relatively low levels of the antigen. 17D6-positive cells also were detected in the peripheral blood of infectious mononucleosis (IM) patients. 17D6-positive cells could be detected in the peripheral blood of a patient with chronic EBV infection at higher levels than in patients with acute IM. After recovery, no 17D6-positive cells could be detected. Radioimmunoprecipitation studies suggested that the 17D6 antibody recognizes a polypeptide of 40,000 mol wt. The results indicated that the 17D6 antibody recognizes an EBV-associated transformation antigen on the surface of in vitro and in vivo infected cells. (4 Refs)

45. MONOCLONAL ANTIBODIES DETECTING EPSTEIN-BARR VIRUS STRAIN AND GROUP SPECIFIC ANTIGENIC DETERMINANTS.

Herbst H, Georg-Fries B, Muller-Lantzsch N, Hausen HZ, Braun DG

Pharmaceuticals Res. Div., CIBA-GEIGY, Basel, Switzerland

Protides Biol Fluid Proc Colloq; 29:735-738 1982

The ability of monoclonal antibodies to detect common and group- and strain-specific antigenic sites on Epstein-Barr virus (EBV) proteins was examined. The EBV strain QIMR-WIL expressing four major envelope polypeptides of mol wt 80,000 (p80), 140,000 (p140), 240,000 (p240), and 340,000 (p340) was used for immunization. Ten of 144 culture supernatants exhibited clearly positive reactions, while 21 gave a weak immunofluorescence. One culture fluid precipitated polypeptide p80 exclusively, while others after cloning precipitated selectively p140, p340, or p240/p340 in combination. Cross-reactions with corresponding polypeptides of EBV strains P3HR-1 and B95-8 were studied. It was suggested that monoclonal antibodies can provide a serological basis for EBV typing. (9 Refs)

46. ANTIBODY PATTERN TO HUMAN CYTOMEGALOVIRUS IN PATIENTS WITH ADENOCARCINOMA OF THE COLON.

Avni A, Haikin H, Feuchtwanger MM, Sacks M, Naggan L, Sarov B, Sarov I

(c/o I. Sarov) Virology Unit, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheva, Israel

Intervirology; 16(4):244-249 1981

The role of human cytomegalovirus (CMV) was examined according to serological patterns in 37 patients with adenocarcinoma of the colon (ACC). The sera were examined for the presence of IgG antibodies by the immunoperoxidase antibody to membrane antigen (IPAMA) method and by the complement-fixation (CF) test. Antibody determinations were also performed by the IPAMA method for three other members of the herpesvirus group: Epstein-Barr virus (EBV), herpes simplex virus (HSV) and varicella-zoster virus (VZV). Comparison groups included normal subjects, ACC patients treated with chemotherapy, and patients operated on for benign diseases. No significant difference was found in the geometric mean titers (GMTs) for CMV and the other herpesvirus in the sera of nontreated ACC patients when compared with the control groups. However, a significantly elevated antibody titer to CMV was found in chemotherapy-treated ACC patients by both the IPAMA and CF methods. In this group, elevated titers were found by the IPAMA method for EBV and HSV, but not for VZV. The significance of serological studies in elucidating the role of CMV in ACC patients is discussed. (Author abstract) (30 Refs)

47. CELL-MEDIATED IMMUNITY IN WART INFECTION.

Thivolet J, Viac J, Staquet MJ

Dept. Dermatology, INSERM, Hopital Edouard Herriot, 69374 Lyon, France

Int J Dermatol; 21(2):94-98 1982

An in vivo test of cell-mediated immunity in wart infection was performed by intradermal test (IDT) of patients with warts (125 with plantar or hand, genital, or flat; 25 with regressing or with past history of warts) by injection of 0.1 ml of inactivated human papilloma virus (HPV) suspension containing 1 ug of viral protein. Guinea pigs were primed with whole virions or polypeptides and challenged by IDT. The percentage of positive IDT was higher in patients with present or past warts than in a control group (63 subjects with no past history of warts); children under 5 yr of age all had negative IDT. Patients with regressing or past warts had the highest percentage of positive IDT. Circulating antibodies were altered in patients who had positive IDT; most patients showed wart virus specific antibodies after IDT. Guinea pigs immunized with either HPV particles or polypeptides showed positive skin test reactions to whole virus particles in all cases. At the humoral level, the animals developed specific antibodies without cross reaction between hand and plantar warts. The IDT seemed to be specific and sensitive in humans; the minority of positive patients who had never had warts is probably a result of unnoticed exposure to HPV. (19 Refs)

48. NATURAL ANTIBODIES TO THE STRUCTURAL CORE PROTEIN (P24) OF THE HUMAN T-CELL LEUKEMIA (LYMPHOMA) RETROVIRUS FOUND IN SERA OF LEUKEMIA PATIENTS IN JAPAN.

Kalyanaraman VS, Sarngadharan MG, Nakao Y, Ito Y, Aoki T, Gallo RC

(c/o Gallo) Lab Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205

Proc Natl Acad Sci USA; 79(5):1653-1657 1982

We investigated the involvement (in adult T-cell leukemias and lymphomas) of the human T-cell leukemia virus (HTLV) that was previously isolated in one of our laboratories from cultured T cells of some patients in the United States with leukemias and lymphomas involving relatively mature T cells. High titers of antibodies capable of quantitative precipitation of 125I-labeled p24, a well characterized core protein of HTLV, were detected in 12 of 12 patients with untreated adult T-cell leukemia (ATL). (1 negative was a patient on chemotherapy). Ten of the 12 positive samples were from an area where the disease is endemic. Strong precipitating antibodies were also detected in five of seven cases of T-cell malignant lymphoma (TML) which differs from ATL by having fewer leukemic cells in the peripheral blood. High antibody titers were also observed in one of five cases of acute monoblastic leukemia and one of eight cases of chronic myelogenous leukemia in the blast phase of the disease. Low to moderate titers of antibodies were detected in several categories of leukemia (2 cases of blast-phase chronic myelogenous leukemia, 2 cases of acute lymphoblastic leukemia of the null-cell type, and 1 case of acute myelogenous leukemia). Among all categories of leukemias, except ATL and TML, more cases were negative than positive for anti-p24 activity. All of 79 sera from normal Japanese, including 39 collected from the endemic ATL area of southwest Japan, were negative for antibodies to HTLV p24. All the positive reactivities observed were highly specific to HTLV. The only competition observed in the precipitation of HTLV p24 was with HTLV or with cell lines expressing HTLV and not with various animal retroviruses or a large number of human and subhuman primate cell lines, not known to be producing HTLV. The data strongly indicate an association of HTLV with the increased incidence of ATL in parts of Japan, probably with other forms of leukemias in Japan, and, less commonly, with certain T-cell malignancies in the United States. (26 Refs)

VIRAL STUDIES IN HUMAN CANCER

49. VULVAR INTRAEPITHELIAL NEOPLASIA: THE CONCEPT AND ITS APPLICATION.

Crum CP

Div. Obstetrical and Gynecological Pathology, Columbia Univ. Coll. Physicians and Surgeons, 630 West 168th St., New York, NY, 10032

Hum Pathol; 13(3):187-189 1982

The role of herpes simplex virus type 2 and human papilloma virus (HPV) in vulvar intraepithelial neoplasia (VIN) are discussed. Diagnosis and classification of VIN based on immunoperoxidase localization of HPV antigens and Feulgen DNA microspectrophotometric technics are described. Use of the technic allows non-neoplastic or infectious processes to be distinguished from VIN. The clinical approach to VIN is discussed. Local removal of lesions by local excision, skinning vulvectomy, and laser with adequate follow-up are commonly used to treat VIN. 5-Fluorouracil treatment of VIN has met with limited success. (24 Refs)

50. GENITAL HERPES INFECTION. CLINICAL AND THERAPEUTIC EFFECTS.

Pelisse M
Hopital Necker, 149, rue de Sevres, F 75730 Paris, France
Gynecologie; 32(4/5):437-440 1981

Genital herpes has been estimated to affect 18-50% of the population and in 85-90% it is due to sexually transmitted herpes Type II virus (HTIIV). In 30-40% of the cases, the primary infection will recur and patients who harbor the virus in the sacral ganglion may excrete it periodically despite the presence of circulating antibodies. The pregnant woman is more susceptible to the virus since 1% have discernible infections compared to 0.3% among women who are not pregnant. Neonatal infection with genital herpes is lethal in 50% of the cases. Serologic studies of neutralizing antibodies have shown a much greater frequency of anti-HTIIV antibodies among women with cervical cancer than in control groups. The risk of dysplasia is considered 2x greater and the risk of cancer is 8x greater in women who have HTIIV. The process of malignant transformation of cervical cells by the virus is associated with the synthesis of new proteins which can be demonstrated by complement fixation. The antibodies can only be detected in women with cervical cancer, and they disappear after the patient is cured. There is no known cure for recurrent HTIIV. (11 Refs) (In FRE)

51. EPIDEMIOLOGIC ASPECTS OF GENITAL HERPES INFECTION.

Fari A, Pelisse M, Trevoux R, Verges J, Gorins A, Peretz M
Laboratorie de la Scala, 137, rue de Vaugirard, F 75015 Paris, France
Gynecologie; 32(4/5):441-445 1981

Of 101 cases of genital herpes simplex virus (GHSV), 85 were Type II and 16 were Type I. The site most often affected was the vulva (84), followed by the cervix (60) and the anus or perianal region (24). Women under 30 yr old were more often affected (58%) than older women. In 19 patients GHSV was the only transmitted disease (STD). In 39 patients, GHSV was associated with one other STD, and in 35 patients, GHSV was associated with two other STD. In eight patients, GHSV was associated with more than two other STD. In 19/56 patients, the herpes virus was able to be isolated from the initial genital lesion more than 2 wk after the onset of the acute episode. In 54 cases where sexual partners were able to be examined, four (7%) tested positive for GHSV. GHSV has been directly correlated to sexual activity and to infection with other STD. Herpetic infections can also exist in patients who have not demonstrated clinical signs of the disease. There is currently no known cure for GHSV. Sexual hygiene, early diagnosis, and the study of immunologic control of the infection are recommended methods at patient protection. (18 Refs) (In FRE)

52. GENITAL HERPES INFECTIONS: DIAGNOSIS AND MANAGEMENT.

Kellum MD, Loucks A
No affiliation given
Nurse Pract; 7(2):14,16,18,21 1982

Viral epidemiology and diagnosis and treatment of genital herpes are reviewed. Of the five herpes viruses which affect humans, clinical studies have shown herpes simplex virus type II to be the causative agent in approx 85% of genital and perineal lesions, the balance apparently due to herpes simplex type I. Current diagnostic and treatment procedures for genital herpes are compared in terms of effectiveness. Importance of the role of the nurse practitioner in client education, counseling, and prevention is emphasized. (13 Refs)

53. THE EPIDEMIOLOGY, MORPHOLOGY, AND COURSE OF CERVICAL CONDYLOMAS.

de Brux J, Ionesco M, Cochard B, Masson MF, Kaeding H, Wolff J, Lievaux M, Prade M, Scali M, Peretz M, Pellissier C, Suchet H

Institut de Pathologie et de Cytologie Appliquee, 53, rue des Belles-Feuilles, F 75116 Paris, France

Gynecologie; 32(4/5):413-418 1981

Of 1,953 suspected condylomatous lesions, 171 (8%) were considered to be severely dysplastic or carcinomatous. Biopsy confirmed the diagnosis in 119/171 cases. Of these 119 cases, 15 were judged moderately severe on the basis of cytologic examination whereas histological examination following biopsy showed them to be severely dysplastic or carcinomatous. Of those patients who were able to be treated and followed, complete regression was obtained between 3-8 mo for eight patients with severe dysplasia. In 14 cases, aggravation led to a carcinoma with invasion (1) and recurrence (2) in 3-14 mo. In five cases, there was partial regression followed by aggravation in three patients during pregnancy. The cytology and histology of condylomatous lesions are thoroughly reviewed, and the viral origins of the lesions are discussed. In order to judge the viral origins of the lesions, a complete study with the participation of cytologists, virologists, histopathologists, and clinicians is recommended. Immediate preventive treatment is suggested in the form of sexual prophylaxis and hygiene. (21 Refs) (In FRE)

54. FINAL CASE REPORTING FROM THE UGANDAN PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN EBV AND BURKITT'S LYMPHOMA.

Geser A, DeThe G, Lenoir G, Day NE, Williams EH

International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon, France

Int J Cancer; 29(4):397-400 1982

A prospective epidemiological study was carried out in the West Nile District of Uganda from 1972 to 1979 in order to investigate the etiological role of the Epstein-Barr virus (EBV) in Burkitt's lymphoma (BL). By 1976, 14 BL cases had been detected among the 42,000 children originally bled in the study area. Testing of sera from BL candidates and neighborhood controls showed that children who develop BL later have EBV/VCA titers several dilutions higher than their age- and sex-matched neighbors. This appearance of a strong EBV activity long before BL development was taken as evidence of a causal role of EBV in BL in order to add to the unique material of pre-bled BL cases, BL detection was continued up to March 1979 when field work became impossible in Uganda. Two additional pre-bled BL cases were found during this extension of the study. The serological and virological evaluation of these additional cases showed that the EBV/VCA titers, but not the EA and EBNA titers, were about two dilutions higher in the BL candidates than in the controls. Hybridization assays showed that both lymphomas contained EBV/DNA in the tumor cells. These additional results thus confirm the findings in the first 14 cases and strengthen the epidemiological evidence for a causal role of the EBV in endemic BL. (Author abstract) (10 Refs)

55. CAUSES OF LEUKEMIAS AND CANCER: RECENT PROGRESS.

Bernard J
bd. de Perolles 53, 1700 Fribourg, Switzerland
Rev Med Suisse Romande; 102(1):95-103 1982

Roles of viruses, radiation, and toxic chemical substances in the development of cancer are discussed. Burkitt's lymphoma (BL), a B-cell lymphoma predominantly localized in facial bones and found most frequently in certain areas of Africa, was one of the first cancers to be related to a virus, Epstein Barr virus (EBV). EBV virus and its antibodies are found in BL patients. EBV virus, the infective agent in mononucleosis, has been shown to cause BL in marmosets. BL shows high correlations with geographic areas with levels of malaria, with chromosome translocation 8:14, and with lower socioeconomic groups. Viruses have also been implicated in cervix cancer (herpes virus), liver cancer (hepatitis B), and Hodgkin's disease. Evidence of radiation-induced cancers has been gained from studies of physicians, radiologists, and scientists exposed to radiation and of Hiroshima survivors. The relationship between radiation and cancer development is significant but varies among individuals. Dietary factors, such as tobacco (lung, bladder, and digestive cancers), alcohol (cirrhosis and liver cancer), and diet in general (high lipid diet and breast cancer) have been related to increased incidences of cancer. Leukemia has been observed in Hodgkin's disease patients treated with chemotherapy. A high incidence of lymphomas has been noted in patients who have undergone organ transplants. The role of heredity and geography in the etiology of cancer is discussed. (no Refs) (In FRE)

56. OUTBREAK OF KAPOSI'S SARCOMA WITH CYTOMEGALOVIRUS INFECTION IN YOUNG HOMOSEXUAL MEN.

Urmacher C, Myskowski P, Ochoa M, Kris M, Safai B
Memorial Hosp., 1275 York Ave., New York, NY, 10021
Am J Med; 72(4):569-575 1982

Kaposi's sarcoma, a multicentric malignant neoplasm, occurs in certain geographic areas in the world. It is most common in Equatorial Africa and Eastern Europe. The annual incidence of Kaposi's sarcoma in the United States is between 0.021 and 0.061 per 100,000 persons. The appearance of an outbreak of Kaposi's sarcoma in young homosexual men in New York and California is a new and unique phenomenon. Certain differences are already recognized between the disease in these young men and the ordinary Kaposi's sarcoma. Herein we report our observations of the first 10 cases of Kaposi's sarcoma in young homosexual men. In these patients, the disease follows an aggressive clinical course characterized by widespread skin lesions with early involvement of the lymph nodes. In some of these patients, the result was death in a short period of time after initial diagnosis. In addition, cytomegalovirus infections were seen in these patients, which suggests at least a possible association between this virus and the disease. (Author abstract) (17 Refs)

57. HUMAN PAPILLOMAVIRUS AND ONCOGENESIS.

Jablonska S
Dermatologische Klinik, Koszykowa 82 A, P-02-008 Warszawa, Poland
Z Hautkr; 57(8):551-552,555-560,563,566 1982

Human papillomaviruses (PV) and oncogenesis were discussed, and the following aspects were included oncogenic properties of animal PV, carcinomas and human PV (PV of larynx in children, genital warts, cervical dysplasia, Bowen's disease, epidermodysplasia verruciformis (EV), the EV induced by human PV-3 and PV-5, cellular immunity (CI), specific CI, and specific humoral immunity), and genetics (importance of determination of types of human PV). (72 Refs) (In GER)

58. HUMAN PAPILLOMAVIRUS DNA IN CUTANEOUS PRIMARY AND METASTASIZED SQUAMOUS CELL CARCINOMAS FROM PATIENTS WITH EPIDERMODYSPLASIA VERRUCIFORMIS.

Ostrow RS, Bender M, Niimura M, Seki T, Kawashima M, Pass F, Faras AJ
Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Proc Natl Acad Sci USA; 79(5):1634-1638 1982

DNA extracted from squamous cell carcinomas from patients with the chronic wart disease syndrome, epidermodysplasia verruciformis, was analyzed for the presence of human papillomavirus (HPV)-specific DNA sequences by Southern blot hybridization analysis. Employing an HPV probe obtained by molecular cloning of viral DNA purified from benign warts from these patients, we have unequivocally identified HPV-specific nucleotide sequences in squamous cell carcinomas from these patients. Restriction endonuclease mapping indicated that the DNA present in the carcinomas was of the same type (Type 5) as that found in the benign tumors from these patients and was present as unintegrated, free viral DNA. Moreover, we have demonstrated the presence of HPV-5 DNA in a subcutaneous metastatic tumor from one of these patients. This latter observation essentially eliminates the possibility that the HPV-5 DNA present in the malignant tumors in these patients resulted from cross-contamination from an adjacent benign warty lesion. In addition to wild-type HPV-5 DNA, both the primary and metastatic carcinomas analyzed also contained an HPV-5 DNA species lacking approximately 20% of the HPV-5 DNA genome. These subgenomic forms of HPV-5 DNA could not be detected in benign papillomas from these patients. (Author abstract) (25 Refs)

59. HEPATITIS B INFECTION AND THE PREVENTION OF PRIMARY HEPATOCELLULAR CARCINOMA: STUDIES IN SENEGAL.

Froment A, Larouze B, Feret E, Marinier E, Moustapha Sow A, London WT, Blumberg BS
(c/o Blumberg) Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Prog Med Virol; 27:133-136 1981

Continuing studies of hepatitis B (HBV) infection in Senegal include mother to child infection antigenic studies, studies of whole villages and family units within them, family studies of patients with primary hepatocellular carcinoma and families with cirrhosis or chronic active hepatitis, and studies of the interaction of protein-calorie malnutrition in children with responses to HBV. Early administration of vaccine could drastically reduce the incidence of HBV, although its effect on malnourished children is unpredictable. (11 Refs)

60. DIFFERENTIAL EXPRESSION OF THE AMV GENE IN HUMAN HEMATOPOIETIC CELLS.

Westin EH, Gallo RC, Arya SK, Eva A, Souza LM, Baluda MA, Aaronson SA, Wong-Staal F

Lab. Tumor Cell Biology, Div. Cancer Treatment, NCI, Bethesda, MD, 20205

Proc Natl Acad Sci USA; 79(7):2194-2198 1982

Total cellular RNAs from a variety of fresh and culture-derived human hematopoietic neoplastic cell types at various stages of differentiation and human sarcoma, carcinoma, melanoma, and glioblastoma cell lines were enriched for poly(A)-containing sequences, fractionated by gel electrophoresis, and blot hybridized to a cloned DNA probe containing the transforming sequences (v-amv) of avian myeloblastosis virus (AMV), a virus known to cause myeloid leukemias in chickens. Expression of RNA sequences homologous to AMV was detected in all immature myeloid and lymphoid T cells in addition to single erythroid cell line examined, but not in mature T cells or in B cells, including lymphoblast cell lines derived from patients with Burkitt lymphoma. In addition, induction of the cell line HL60, a promyelocytic leukemia line, to differentiate with dimethyl sulfoxide or retinoic acid resulted in a reduction of the level of expression of the human cellular gene c-amv homologous to v-amv. There was no detectable c-amv mRNA in any of the solid tumor cell lines examined. Thus, expression of the human c-amv gene could be correlated with the stage of differentiation of different hematopoietic cell types determines by morphologic and marker studies. Expression of c-amv could not be correlated with the extent of methylation in HL60 and in HL60 induced to differentiate with dimethyl sulfoxide. (Author abstract) (48 Refs)

61. ISOLATION AND CHARACTERIZATION OF RETROVIRUS FROM CELL LINES OF HUMAN ADULT T-CELL LEUKEMIA AND ITS IMPLICATION IN THE DISEASE.

Yoshida M, Miyoshi I, Hinuma Y

Dept. Viral Oncology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan

Proc Natl Acad Sci USA; 79(6,part1):2031-2035 1982

A retrovirus (ATLV) was unequivocally demonstrated in human adult T-cell leukemia (ATL) cell lines by density (1.152-1.155 g/cm3) in a sucrose gradient, reverse transcriptase activity insensitive to actinomycin D, RNA labeled with [3H]uridine, and specific proteins with mol wt of 11,000, 14,000, 17,000, 24,000, and 45,000. Furthermore, cDNA prepared by endogenous reaction with detergent-treated virions hybridized to 35S RNA containing poly(A), which was inducible by IdUrd treatment of a T-cell line derived from leukemic cells of the ATL, and the integrated form of ATLV proviral DNA was detected in T-cell lines derived from ATL. The ATLV proviral DNA was also detected in fresh peripheral lymphocytes from all five patients with ATL tested so far but not in those from healthy adults. On the other hand, ATLV protein of Mr 42,000 was found to be at least one of the ATL-associated antigen(s) that were previously detected in ATL leukemic cells by all sera from patients with ATL. These findings on the close association of ATLV protein and proviral DNA with ATL are direct evidence for the possible involvement of the retrovirus ATLV in leukemogenesis of human ATL. (Author abstract) (18 Refs)

62. ADULT T-CELL LYMPHOMA-LEUKAEMIA IN BLACKS FROM THE WEST INDIES.

Catovsky D, Rose M, Goolden AW, White JM, Bourikas G, Brownell AI, Blattner WA, Greaves MF, Galton DA, McCluskey DR, Lampert I, Ireland R, Bridges JM, Gallo RC

Medical Res. Council Leukaemia Unit, Royal Postgraduate Medical Sch., London, England

Lancet; 1(8273):639-642 1982

Six Black patients (5 born in the West Indies and 1 in Guyana), aged 21-55 yr, had adult T-cell lymphoma-leukemia diagnosed in the UK This disorder is rare in Europe and the USA, but is more common in Japan. Five patients had severe hypercalcemia which correlated with disease activity, although osteolytic lesions were found in only one. Other clinical features were lymphadenopathy and a high white blood-cell count (range 27-67 x 10(9)/l) with a predominance of pleomorphic lymphoid cells with pronounced nuclear irregularities prominent at ultrastructural level. The cells in all cases formed rosettes with sheep red blood-cells and lacked terminal transferase. Analysis with OKT monoclonal antibodies in four cases confirmed a mature T-cell phenotype defined as helper/inducer (T4+, T6-, T8-) in three. Combination chemotherapy resulted in short-lived remissions; four patients died and two have survived 3-6 mo. The disease in these patients is indistinguishable on clinical and pathological grounds from adult T-cell leukemia/lymphoma in Japan. Geographical clustering among certain racial groups suggests common etiological factors in the pathogenesis of this disease. The finding of high titer antibody against the structural core protein (p24) of a new human C-type leukemia virus (human T-cell leukemia/lymphoma virus) in all tested cases from this series and data from all but one case from Japan suggest that one such factor may be viral. (Author abstract) (no Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

63. INTRAVENOUS ACYCLOVIR TREATMENT FOR PRIMARY GENITAL HERPES.

Mindel A, Adler MW, Sutherland S, Fiddian AP

Academic Dept. Genito-Urinary Medicine, Middlesex Hosp. Medical Sch., London W1, England

Lancet; 1(8274):697-700 1982

Thirty patients with a severe first attack of genital herpes were treated with intravenous acyclovir in a randomized, double-blind, placebo-controlled trial. The medians for healing time, duration of vesicles, new lesion formation, viral shedding, and all symptoms were significantly shorter in patients treated with acyclovir than in the controls. No important side-effects were noted. Intravenous acyclovir seems to be a safe and effective therapy for patients having their first attack of genital herpes. (Author abstract) (13 Refs)

64. ALPHA INTERFERON AND ACYCLOVIR TREATMENT OF HERPES SIMPLEX VIRUS IN LYMPHOID CELL CULTURES.

Hammer SM, Kaplan JC, Lowe BR, Hirsch MS
Infectious Disease Unit, Dept. Medicine, Massachusetts General Hosp., Boston, MA, 02114
Antimicrob Agents Chemother; 21(4):634-640 1982

The T-lymphoblastoid cell line CEM, persistently infected with herpes simplex virus type 1, has been used to examine the antiviral efficacy of human alpha interferon and acyclovir, both alone and in combination. Acyclovir and interferon each produced dose-dependent decreases in virus titer at concentration ranges of 1 to 100 uM (approx 0.225 to 22.5 ug/ml) and 10 to 10,000 U/ml, respectively. Mean reductions in titer of 1.9 and 4.2 log10 PFU/ml were observed with 100 uM acyclovir and 10,000 U of interferon per ml, respectively, on day 10 of treatment. The combination of 100 uM acyclovir and 10,000 U of interferon per ml produced the most rapid fall in virus titer of all regimens examined and elimination of infectious virus by day 7. Prolonged treatment (greater than 10 days) with acyclovir or alpha interferon was accompanied by a gradual return of virus titer to control levels despite the continuous presence of drug. Virus preparations isolated from such cultures were tested for antiviral agent sensitivity by a plaque reduction method. Acyclovir-exposed isolates were found to be acyclovir resistant, with 50% inhibitory doses of greater than 200 uM, and to be thymidine kinase deficient. Alpha interferon-exposed isolates were not interferon resistant. These results suggest that, in persistently herpes simplex virus-infected CEM cells: (i) combination treatment with 100 uM acyclovir and 10,000 U of alpha interferon per ml is more effective in reducing virus titer than either agent alone; (ii) prolonged exposure to drug may result in development of resistance by either the virus strain or the host cell system; and (iii) development of acyclovir resistance by herpes simplex virus in lymphoid cells is mediated by thymidine kinase. (Author abstract) (37 Refs)

65. ACYCLOVIR TREATMENT OF HERPES ZOSTER INFECTIONS. USE IN CHILDREN UNDERGOING BONE MARROW TRANSPLANTATION.

Serota FT, Starr SE, Bryan CK, Koch PA, Plotkin SA, August CS
Bone Marrow Transplantation Unit, Children's Hosp. Philadelphia, 34th St. and Civic Center Blvd., Philadelphia, PA, 19104
JAMA; 247(15):2132-2135 1982

Three patients in whom herpes zoster infections developed following bone marrow transplantation were treated with acyclovir. The patients experienced pain relief within 24 hr of starting treatment. The progression of their skin lesions halted within 1, 2, and 4 days of therapy, respectively, and healed completely within 2 wk of therapy. Pharmacokinetic studies indicated that acyclovir plasma concentration-time profiles approximated biexponential equations. The drug half-lives were 3.91, 3.83, and 3.40 hr, respectively. Acyclovir was not myelotoxic and may be helpful in aborting varicella-zoster virus infections in bone marrow transplant recipients. (Author abstract) (10 Refs)

66. TOPICAL POLYRIBOINOSINIC-POLYRIBOCYTIDYLIC ACID COMPLEX IN THE TREATMENT OF RECURRENT GENITAL HERPES.

Crane LR, Levy HB, Lerner AM
(c/o Lerner), Hutzel Hosp. Medical Unit, Detroit, MI, 48201
Antimicrob Agents Chemother; 21(3):481-485 1982

Polyriboinosinic-polyribocytidylic acid complexed with poly-l-lysine and carboxymethylcellulose [poly(ICLC)] is a potent interferon inducer when given parenterally to humans. Topical application in animal models has shown beneficial antiviral and clinical effects. In a randomized, double-blinded, placebo-controlled trial of topical poly(ICLC) in recurrent genital herpes simplex virus infection, five clinical and two virological parameters were followed. Fifty-seven men and women, with 78 recurrences of genital herpes, were stratified by sex. No clinical or antiviral differences between poly(ICLC) and placebo groups in either stratum were found. Further analysis of male subgroups by age and size of lesions showed no changes in the rapidity of healing or viral shedding. (Author abstract) (7 Refs)

67. TREATMENT OF HERPES GENITALIS.

Singha HS, Nasr MS
Dept. Genito-Urinary Medicine, Royal South Hants Hosp., Bullar St., Southampton, England
J Int Med Res; 10(1):39-41 1982

The value of povidone-iodine formulations for genital herpes treatment is reviewed with specific reference to primary herpes simplex type 2 infection. Four groups of 25 patients with genital herpes were treated with dimethylsulfoxide (DMSO), Idoxuridine or povidone-iodine (Betadine antiseptic paint). All patients treated with DMSO and Betadine paint had completely healed lesions after 2 wk of treatment, while two patients treated with Idoxuridine did not show complete healing. Topical use of povidone-iodine appears to be an effective treatment and should result in a decrease in secondary infection. (7 Refs)

68. INHIBITION OF HERPES SIMPLEX VIRUS REPLICATION BY SUCCINYL CONCANAVALIN A.

Garrity P, Szelc C, Paquette C, McEvoy M, Millette R, Adler R
Dept. Natural Sciences, Univ. Michigan-Dearborn, Dearborn, MI, 48128
Antimicrob Agents Chemother; 21(3):450-455 1982

Incubation of herpes simplex virus Type 1-infected cells with succinyl-concanavalin A, a derivative of the jack bean lectin concanavalin A, resulted in the decreased production of virus. The mode of inhibition by the lectin was unclear. No effect was apparent on the level of viral DNA synthesis. However, incubation of infected cells with increasing concentrations of the lectin appeared to result in a decrease in the quantity of viral protein produced within the cell. A reduction in the virus titer of 57 to 64% was observed upon direct incubation of extracellular virus in the presence of 50 to 100 ug of succinyl-concanavalin A per ml. (Author abstract) (35 Refs)

69. COMPARATIVE EFFICACY OF ANTIHERPES DRUGS IN DIFFERENT CELL LINES.

De Clercq E
Rega Inst. Medical Res., Univ. Leuven, B-3000 Leuven, Belgium
Antimicrob Agents Chemother; 21(4):661-663 1982

A selection of antiherpes compounds including bromovinyldeoxyuridine (BVDU), acyclovir (ACV), and fluoroiodoaracytosine (FIAC) were compared for their inhibitory effects on herpes simplex virus type 1 (strain KOS) replication in a wide variety of human, simian, feline, and murine cell lines. The 50% inhibitory doses of the compounds varied considerably from one cell line to another, ie, from 0.01 to 2 ug/ml for ACV and from 0.004 to 0.2 ug/ml for BVDU and FIAC. However, the relative order of antiviral potency remained constant, thus (in order of decreasing potency) BVDU greater than FIAC greater than ACV, for all cell lines studied except for the murine embryo cells, in which the order of decreasing potency was BVDU greater than ACV greater than FIAC, and for the feline lung cells, in which the order of decreasing potency was FIAC greater than ACV greater than BVDU. (Author abstract) (10 Refs)

70. INTERVENING EFFECT OF L-ASCORBIC ACID ON EPSTEIN-BARR VIRUS ACTIVATION IN HUMAN LYMPHOBLASTOID CELLS AND ITS COMPARISON WITH THE EFFECT OF RETINOIC ACID.

Morigaki T, Ito Y
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Cancer Lett; 15(3):255-259 1982

Inhibitory effects of L-ascorbic acid (AA) on the induction of Epstein-Barr virus (EBV)-associated antigens in human lymphoblastoid P3HR-1 and Raji cells latently infected with EBV were studied. The effect of AA was compared with the inhibitory effect of retinoic acid (RA) in the same system; the intervening activity of AA was weaker but its cytotoxicity was remarkably lower than that of RA. The effect of AA in varying concentrations (0.1-1,000 uM) on the induction of EBV early antigen and viral capsid antigen in the producer P3HR-1 cell system by single use of 5-iododeoxyuridine, n-butyrate, or 12-O-tetradecanoyl-phorbol-13-acetate is illustrated. (10 Refs)

GENERAL REVIEWS

71. HERPESVIRIDAE: DEFINITION, PROVISIONAL NOMENCLATURE, AND TAXONOMY.

Roizman B, Carmichael LE, Deinhardt F, De-The G, Nahmias AJ, Plowright W, Rapp F, Sheldrick P, Takahashi M, Wolf K
Marjorie B. Kovler Viral Oncology Laboratories, 910 E. 58th St., Chicago, IL, 60637
Intervirology; 16(4):201-217 1981

Description of the family Herpesviridae is followed by the naming and classification of herpesviruses. A provisional designation and classification is presented in tabular form of viruses of man, non-human primates, those of other mammals, birds, reptiles, amphibians and bony fishes. Further classifications are presented based on biologic properties and properties of genomes. A classification of selected herpesviruses into subfamilies and genera is also presented. (136 Refs)

OTHER RELATED STUDIES

72. HUMAN LEUKOCYTE INTERFERON FOR THE TREATMENT OF VARICELLA IN CHILDREN WITH CANCER.

Arvin AM, Kushner JH, Feldman S, Baehner RL, Hammond D, Merigan TC
Dept. Pediatrics, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
N Engl J Med; 306(13):761-765 1982

Results of interferon (IF) treatment of varicella (VA) in children with cancer (CA) are presented. Forty-four patients with CA and VA were enrolled in two consecutive randomized, double-blind placebo-controlled trials. Patients were eligible for the study if they were receiving chemotherapy at the onset of VA or they had received radiation therapy within the preceding mo, and if treatment could be instituted within 72 hr after the appearance of exanthem. Nine of the 18 patients enrolled in the initial trial (1974-1977) received IF at doses of 4.2 x 10(4) to 2.5 x 10(5) units (U)/kg body wt/day until no new vesicles had appeared for 24 hr. The av duration of therapy was 6.4 days. In the second trial (1978-1981) 14 of 26 patients received IF at an initial dose of 3.5 x 10(5) U/kg body wt/day for 48 hr, followed by 1.75 x 10(5) U/kg body wt/day for 72 hr. The IF and placebo groups were compared with respect to underlying disease, number of days from onset of VA to enrollment in the study, number of lesions at entry, and initial white-cell and platelet counts. Sixteen of 23 IF recipients and 14/21 placebo recipients had acute lymphocytic leukemia. Treatment with IF had a significant effect on the number of days of new lesion formation in immunocompromised patients with VA. Ninety percent of IF recipients had no new lesions for at least 24 hr by day 7 after enrollment, compared with 56% of placebo recipients. The overall incidence of fatal and life-threatening VA was 8.7% (2/23) in the IF group and 28.6% (6/21) in the placebo group. Results indicate that IF has an antiviral effect against VA virus in immunocompromised patients. (13 Refs)

73. THE EFFECT OF HYPERTONIC SALT ON INTERFERON AND INTERFERON MRNA SYNTHESIS IN HUMAN MG63 CELLS.

Meager A, Shuttleworth J, Just MD, Boseley P, Morser J
Div. Viral Products, Natl. Inst. Biological Standards and Control, Holly Hill Hampstead, London NW3 6RB, England
J Gen Virol; 59(part1):177-181 1982

After infection with Sendai virus or Newcastle disease virus (NDV) Strain F, human osteosarcoma MG63 cells produced large amounts of interferon-beta. Both interferon production and overall protein synthesis was strongly inhibited by hypertonic salt. Interferon mRNA synthesis, however, was little affected by hypertonic salt up to twice normal salt concentrations, although cellular RNA synthesis was inhibited under these conditions. The results are compared to those obtained with polyriboinosinic acid:polyribocytidylic acid copolymer [poly(rI)-poly(rC)] inductions of MG63 cells. (Author abstract) (14 Refs)

74. REACTIVATION OF UV- AND GAMMA-IRRADIATED HERPES VIRUS IN UV- AND X-IRRADIATED CV-1 CELLS.

Takimoto K, Niwa O, Sugahara T
Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Photochem Photobiol; 35(4):495-499 1982

Enhanced reactivation of UV- and gamma-irradiated herpes virus was investigated by the plaque assay on CV-1 monkey kidney monolayer cells irradiated with UV light or x-rays. Both UV- and x-irradiated CV-1 cells showed enhancement of survival of UV-irradiated virus, while little or no enhancement was detected for gamma-irradiated virus assayed on UV- or x-irradiated cells. The enhanced reactivation of UV-irradiated virus was greater when virus infection was delayed 24 or 48 hr, than for infection immediately following the irradiation of cells. It is demonstrable that the UV- or x-irradiated CV-1 cells are able to enhance the repair of UV damaged herpes virus DNA, but not of gamma-ray damaged ones. (Author abstract) (24 Refs)

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HE 20.3173/2:

VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. ISOLATION AND CHARACTERIZATION OF TWO STRAINS OF HERPESVIRUS HOMINIS TYPE 1 FROM FALLOPIAN TUBES.

Barton IG, Najem SN, Walker MJ, Potter CW
Dept. Virology, Univ. Sheffield Medical Sch., Beech Hill Road, Sheffield S10 2RX, England
J Med Microbiol; 15(1):63-71 1982

Two viruses isolated from fallopian tube biopsy of two patients in different hospitals were characterized. Immunofluorescence tests clearly indicated that the isolates were strains of Herpesvirus hominis type 1 (HSV-1). The two isolate viruses were very similar to HSV-1 strain 71-15 and HSV-2 strain 333 in terms of restriction-enzyme analysis of viral DNA and polypeptide profile; these results were identical upon reisolation after storage in liquid nitrogen. (13 Refs)

2. STRUCTURAL DIFFERENCES BETWEEN HEXONS FROM ADENOVIRUS TYPES 2 AND 5: CORRELATION WITH DIFFERENCES IN SIZE AND IMMUNOLOGICAL PROPERTIES.

Von Bahr-Lindstrom H, Jornvall H, Althin S, Philipson L
Dept. Chemistry I, Karolinska Institutet, Box 60400, S-104 01 Stockholm, Sweden
Virology; 118(2):353-362 1982

The primary structure of the hexon capsid protein from adenovirus Type 5 (Ad5) has been investigated. The carboxymethylated polypeptide was cleaved with CNBr. The resulting fragments were purified and submitted to N-terminal sequence analysis. All large CNBr fragments were recovered and identified. Comparisons with the corresponding Ad2 peptides showed that the two hexon proteins have great similarities. Two regions with sequence differences were, however, identified, containing several amino acid substitutions. In addition, the Ad5 protein contained two major deletions. The smaller size of the Ad5 hexon can therefore be explained by internal deletions rather than by differences in the terminal ends. In accordance, the latter were largely unaltered between the two proteins. The regions that differ contain the trypsin sensitive sites of the native Ad2 hexon, explaining the insensitivity to trypsin of the native Ad5 protein. These sites may contain the type-specific immunological determinants of hexon. (Author abstract) (19 Refs)

3. NEW HUMAN PAPILLOMA VIRUS ISOLATED FROM EPIDERMODYSPLASIA VERRUCIFORMIS LESIONS.

Yutsudo M, Tanigaki T, Tsumori T, Watanabe S, Hakura A
Dept. Tumor Virology, Res. Inst. Microbial Diseases, Osaka Univ., Yamadaoka, Suita 565, Japan
Cancer Res; 42(6):2440-2443 1982

Human papilloma virus (HPV) was isolated from red plaques of a patient (N.F.) with epidermodysplasia verruciformis. Electron microscopic examination showed characteristic particles of papilloma virus as icosahedrons about 45 nm in diameter. DNA was extracted from these particles, and closed-circular DNA (Form I) was purified by centrifugation in CsCl containing ethidium bromide. The molecular weight of the DNA was about 5.0 x 10(6). A physical map of the HPV DNA was constructed using several restriction enzymes. The restriction endonuclease cleavage pattern of the HPV DNA was different from those of other types of HPV reported thus far, suggesting that the isolate was a new, as yet unclassified, HPV. (Author abstract) (29 Refs)

4. DIFFERENT FORMS OF SIMIAN VIRUS 40 LARGE TUMOR ANTIGEN VARYING IN THEIR AFFINITIES FOR DNA.

Gidoni D, Scheller A, Barnet B, Hantzopoulos P, Oren M, Prives C
(c/o Prives) Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
J Virol; 42(2):456-466 1982

In various permissive monkey cell lines infected with simian virus 40 there are two major forms of large T antigen which differ in their rate of sedimentation through sucrose gradients. The lighter (5 to 7S) form sedimented slightly more rapidly than the 4S tRNA marker, whereas the heavier (16S) form sedimented slightly more slowly than the 18S rRNA marker. The small t antigen did not form complexes which sedimented as rapidly as those formed by the large T antigen. The 16S T antigen form was converted to the slowly sedimenting 5 to 7S form in the presence of 1.0 M NaCl. The majority of large T antigen synthesized in cell-free protein-synthesizing systems primed by mRNA isolated from infected cells sedimented as the 5 to 7S form even when premixed with excess quantities of cellular T antigen. The formation of the 16S form in infected cells did not require ongoing viral or cellular DNA replication because considerable quantities of this T antigen class were produced in the presence of DNA synthesis inhibitors, such as cytosine cytosine arabinoside. Both 5 to 7S and 16S forms could be isolated separately and, therefore, each could be analyzed as to its individual properties. The 5 to 7S T antigen form bound more efficiently and tightly to DNA and had specific affinity for sequences at the viral origin of replication, whereas the 16S form bound less efficiently to DNA and exhibited very little specificity for origin-containing DNA sequences. It is therefore likely that the active DNA-binding species of T antigen isolated from infected cells is the 5 to 7S form. (Author abstract) (43 Refs)

5. BIOLOGICAL AND BIOCHEMICAL STUDIES OF AFRICAN GREEN MONKEY LYMPHOTROPIC PAPOVAVIRUS.

Takemoto KK, Furuno A, Kato K, Yoshiike K
Lab. Molecular Microbiology, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
J Virol; 42(2):502-509 1982

The growth of African green monkey lymphotropic papovavirus (LPV) in human lymphoblastoid cell line BJA-B was found to be slow and inefficient due to the accumulation of defective particles. An analysis of molecularly cloned LPV DNAs showed that 3 of 19 clones had DNAs that were longer (5.1 kilobases) than the DNAs of the other clones. The 5.1-kilobase DNA was infectious for BJA-B cells, whereas the shorter (4.8-kilobase) molecules were defective. Unlike the wild-type virus, stocks of LPV made from cloned, infectious DNAs were homogenous and had higher titers. Using stocks of nondefective LPV, we investigated other biological properties. LPV replication in another human B-lymphoblastoid cell line was observed. The virus did not cause tumors when it was inoculated into newborn hamsters. Serological surveys of human and nonhuman primate sera indicated that virtually all primates, including humans, show evidence of infection by viruses antigenically related to LPV. (Author abstract) (29 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

6. HERPES SIMPLEX VIRUS-INDUCED CHANGES IN CELLULAR AND ADENOVIRUS RNA METABOLISM IN AN ADENOVIRUS TYPE 5-TRANSFORMED HUMAN CELL LINE.

Stenberg RM, Pizer LI

(c/o Pizer) Dept. Microbiology, Univ. Colorado Medical Sch., Denverity, CO, 80262

J Virol; 42(2):474-487 1982

We used the viral transcripts (designated Ad-RNA) that accumulated in the cytoplasm of adenovirus Type 5-transformed human embryonic kidney cells (cell line 293-31) as models for cellular RNAs to examine how herpes simplex virus modifies cellular RNA metabolism. Infection of 293-31 cells with herpes simplex virus Type 1 Strain 17 led to extensive inhibition of Ad-RNA accumulation by 4 hr postinfection. The major part of this inhibition was due to an immediate early or alpha gene function, which reduced the rate of transcription of Ad-RNA within the nuclei of the infected cells. In addition, host polyadenylic acid-containing RNA accumulation and rRNA accumulation were affected, but to a lesser extent and at a slower rate than Ad-RNA accumulation. In conjunction with previous data, our experimental data allowed us to propose a general scheme for how herpes simplex virus Type 1 alters the metabolism of cellular RNA, the possible mechanisms for these changes, and how they correlate with the regulation of herpes simplex virus gene expression. (Author abstract) (52 Refs)

7. HERPESVIRUS SAIMIRI-INDUCED LYMPHOMA IN NEW WORLD PRIMATES: TUMOR CELL PHENOTYPE AND VIRUS DISTRIBUTION IN T CELL SUBSETS (MEETING ABSTRACT)

Neubauer RH, Klein RA, Briggs C, Rabin H

National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701

Fed Proc; 41(3):271 1982

Studies using monoclonal antibodies have indicated that the human determinants for the sheep erythrocyte receptor (OKTlla), the helper/inducer T cell marker (leu3a), and HLA-DR (Ia) antigens are conserved among primates. Using these antibodies and fluorescence activated cell sorter analysis, we examined the phenotype of Herpesvirus saimiri-induced lymphomas in New World primates. Results with owl monkeys or marmosets showed that cell lines established from tumors were uniformly OKTlla+ and Ia+ and that the cells could be either leu3a+ or leu3a-; mixed cultures were never observed. In contrast, cell lines of normal T cells were comprised of both leu3a+ and leu3a- cells. Twenty-five percent of owl monkeys inoculated with H saimiri develop a disease-free chronic infection where the virus is associated with the T cells. We examined four such animals to determine if the virus is restricted to a specific T cell subset. Virus was restricted to leu3a+ cells in one animal while in other monkeys it was found equally in leu3a+ and leu3a- populations. Studies designed to look at the phenotype and the localization of virus in fresh tumors are in progress. (no Refs)

8. IN VITRO PRODUCTION OF TUMOR-RELATED HUMAN MONOCLONAL ANTIBODY AND ITS IMMUNOHISTOCHEMICAL SCREENING WITH AUTOLOGOUS TISSUE.

Hirohashi S, Shimosato Y, Ino Y
Pathology Div., Natl. Cancer Center Res. Inst., 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan
Gan; 73(2):345-347 1982

The property of Epstein-Barr virus (EBV) to transform human B lymphocytes into lymphoblastoid cells secreting immunoglobulins was used to obtain human antibodies against human tumors. EBV was taken from the marmoset cell line B95-8. A virus stock was produced by culturing B95-8 cells for 7 days in a medium of RPMI-1640 supplemented with 20% heat inactivated fetal bovine serum, 100 Units/ml penicillin, and 100 ug/ml streptomycin, separating culture supernatants, and filtering through a Millipore filter. Regional lymph nodes were obtained at surgery from a 45-yr-old woman with Dukes' C moderately-differentiated adenocarcinoma of the rectum and from a 37-yr-old man with Borrmann's Type II signet ring cell carcinoma of the stomach. Single cell suspensions were prepared from the lymph nodes, resuspended in culture medium, and then mixed with virus stock. A 0.1 ml portion of the resulting mixture was distributed to 92-well tissue culture plates, cultured for 4 wk, and transferred to 24 other well tissue culture plates for 2 more wk of culturing. Culture supernatants were harvested and screened for the presence of antibody against autologous tumor tissue. In the case of rectal cancer, supernatants from 6/24 well positively stained the autologous tissue. The reaction products were located at the luminal surface of tumor cells, and the distribution was quite similar to that of carcinoembryonic antigen. In the case of gastric cancer, supernatants from 7/24 wells positively stained the autologous tissue. The results demonstrate that human antibodies against human tumors and normal tissues can be produced by EBV transformation of lymphocytes, suggesting that there is potential clinical application of this technique for treating tumors and that lymphocytes producing autoantibodies against normal tissues could be easily cultured from the lymph nodes adjacent to tumors. (6 Refs)

9. CHARACTERIZATION OF IMMUNOGLOBULIN SECRETION BY BURKITT'S LYMPHOMA (BL) CELL LINES (MEETING ABSTRACT)

Benjamin D, Magrath IT, Maguire R, Weiss RB, Blaese M
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:1026 1982

As part of an investigation of the cellular origins of undifferentiated lymphoma (UL) we have studied immunoglobulin (Ig) secretion in cell lines derived from American (AM) and African (AF) BL, Epstein Barr Virus (EBV) transformed cord blood lymphocytes (CBL) and diploid lymphoblastoid cell lines. Ig secretion was monitored by pulse labelling with either 35S-methionine (Me) or 3H-Leucine (Le) followed by immunoprecipitation with polyvalent anti-human Ig antiserum. Twelve of 14 of AM lines secreted exclusively IgM of a single light chain (LC) class but AM lines secreted greater amounts. Nontumor lines secreted multiple heavy and LC classes. Some lines secreted Ig LC which did not contain Me, but was detected by labelling with Le. A significant correlation between the presence of EBV genome and the absence of Me in the secreted Ig was found. Ten of 11 EBV negative lines secreted Me containing LC whereas Me was not detected in 4/5 EBV positive lines. The IgM in the supernatant had a high M Wt consistent with a pentameric structure and was associated with

J chain; features of secreted Ig but not of membrane bound Ig. Free LC were secreted in large amounts in AM lines in contrast to the low amounts detected in AF lines and CBC. Kinetic studies using a Reverse Hemolytic Plaque assay technique have shown that peak of Ig secretion is on the 2nd day after subculturing and only 1% of the cells secrete Ig. Addition of pokeweed mitogen and irradiated B plus T cells or 12-O-Tetradecanoylphorbol 13-Acetate (TPA) induced up to 10 fold increase of Ig secretion in the Am lines. (no Refs)

10. RNA AND PROTEIN SYNTHESIS ARE REQUIRED FOR THE DEVELOPMENT OF INCREASED SENSITIVITY TO NATURAL KILLING IN RAJI CELLS FOLLOWING P3HR-1 VIRUS SUPERINFECTION (MEETING ABSTRACT)

Blazar BA, Fitzgerald J, Strome M
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115
Proc Am Assoc Cancer Res; 23:1057 1982

Sensitivity to natural killing (NK) by normal human peripheral blood lymphocytes develops in normally unsusceptable Raji cells after superinfection with the P3HR-1 strain of Epstein-Barr Virus. This sensitivity to NK is measured as specific 51Cr release in 4 hr assays at 100:1 effector target ratios. NK sensitivity is due to an early membrane change that does not require DNA synthesis since this sensitivity develops in superinfected Raji cells cultured in the presence of cytosine arabinoside (Ara-c) (10 ug/ml). NK sensitivity does not develop in P3HR-1 superinfected Raji cells that are cultured in the presence of the RNA synthesis inhibitor actinomycin D (1 ug/ml) and drops to half the amount usually detected in superinfected cells that are grown with the protein synthesis inhibitor cyclohexamide (50 ug/ml). Removal of the 24 hr cyclohexamide block restores the sensitivity to NK to that of the untreated P3HR-1 infected cells. These findings suggest that the development of NK sensitivity in Raji cells following superinfection is due to the addition to the cell membrane of a virally promoted molecule (s) that requires active RNA and protein synthesis. (no Refs)

11. EPSTEIN-BARR VIRUS (EBV) GENOME IN HUMAN LYMPHOMA CELLS AMPLIFIES EXPRESSION OF THE PROVIRAL MURINE LEUKEMIA VIRUS (MULV) P30 (MEETING ABSTRACT)

Lasky RD, Troy FA
Department of Biol Chem, University of California School of Medicine, Davis, CA, 95616
Fed Proc; 41(3):1387 1982

EBV-negative lymphoma lines, Ramos and BJAB, can be converted in vitro to EBV-positive sublines thus providing a uniclonal tumor cell population in which the same line can be compared with and without the EBV genome. We have used this system to distinguish between trivial subline difference and differences related to the presence of the EBV genome. The antigenic profiles of plasma membranes were examined using sera from immunized rabbits. Tumor cells proteins were resolved by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and then electrophoretically transferred to nitrocellulose paper. Anti-tumor cell sera was allowed to bind to the antigens. Binding was detected using 125I-labeled antibodies to the IgG of the primary sera, followed by autoradiography. Electro-blotting revealed several distinct differences. A major difference was an increase in a 30K dalton protein (p30) in the Ramos converted sublines. In contrast, no p30 seen in BJAB or its converted lines. When Ramos, but not BJAB, was originally established in culture, it was passaged in athymic nude mice and acquired an MuLV provirus. Present results suggested that the EBV-genome in Ramos converted cells amplified expression of the mouse p30. This conclusion was confirmed using antisera specific for MuLV and p30. How EBV is promoting enhancement of retroviral proteins in these human lymphoma cells and its possible biological significance is not clear. (no Refs)

12. CHARACTERIZATION OF TRANSFORMED CELLS AND TUMORS BY PROTON NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY.

Mountford CE, Grossman G, Reid G, Fox RM

Sch. Biochemistry, Univ. New South Wales, P. O. Box 1, Kensington, New South Wales 2033, Australia

Cancer Res; 42(6):2270-2276 1982

Cultured acute lymphoblastic leukemic cells give a well-resolved proton nuclear magnetic resonance spectrum characteristic of isolated plasma membranes. We demonstrate that the signals, in the spectrum of whole cells, arise predominantly from the plasma membrane and that cells transformed by pokeweed mitogen have membranes which are significantly less rigid than are normal human peripheral blood lymphocytes. Normal thymus, malignant thymus, and a leukemic T-cell line have been compared by proton nuclear magnetic resonance spin echo experiments, and the normal thymus was found to differ. Cells transformed by the Epstein-Barr virus can also be characterized and shown to differ from the leukemically transformed cells by spin echo experiments. Since no probe molecule was required to obtain these results, this is the first definitive evidence that the structure and fluidity of the plasma membranes change as a result of transformation of lymphocytes. Proton nuclear magnetic resonance spectroscopy can now be used to compare the effect of different mitogens on T- and B-lymphocytes as well as to monitor the effects of drugs, metals, etc, on the plasma membrane of transformed lymphocytes. (Author abstract) (29 Refs)

13. STUDIES ON ANTIGENS OF A LEUKEMIC NULL-CELL LINE (NALL-1). I. STIMULATORY CAPACITY IN MIXED LYMPHOCYTE CULTURE.

Uno J

Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan

Okayama Igakkai Zasshi; 93(5/6):481-487 1981

A one-way mixed lymphocyte reaction between lymphocytes from normal human donors and mitomycin C-treated cells from a human leukemic null-cell line (NALL-1) was investigated. Human leukemic T-cell and B-cell lines, an Epstein-Barr virus (EBV)-negative Japanese Burkitt's lymphoma line, and two EBV-positive normal B-cell lines were studied in parallel. Normal lymphocytes were stimulated significantly by the cultured null- and B-cells but not by the cultured T-cells. The stimulatory capacity of this null-cell line was approx equal to that of the leukemic, lymphoma, and normal B-cell lines, and was unrelated to the presence of complement receptor, surface immunoglobulin, EBV-associated nuclear antigen, terminal deoxynucleotidyl transferase or the origin of the cell lines. These results suggest that not only leukemic B-cells but also leukemic null-cells have stimulatory determinants in mixed lymphocyte culture. (Author abstract) (21 Refs) (In JPN)

14. MEMBRANE ANTIGEN ON EPSTEIN-BARR VIRUS-INFECTED HUMAN B CELLS RECOGNIZED BY A MONOCLONAL ANTIBODY.

Slovin SF, Frisman DM, Tsoukas CD, Royston I, Baird SM, Wormsley SB, Carson DA, Vaughan JH
(c/o Vaughan) Dept. Clinical Res., Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
Proc Natl Acad Sci USA; 79(8,part1):2649-2653 1982

This paper describes a monoclonal antibody (B532) that detects a membrane antigen present on greater than or equal to 95% of the B cells from lines carrying the Epstein-Barr virus (EBV) genome. Evidence suggesting that B532 is EBV-related was originally obtained by using a cell-binding radioassay with different cell line substrates. Immunofluorescence and cell-sorter analysis confirmed that the antigen was present in high density on all EBV-infected lymphoblastoid B-cell lines, but not on EBV-negative B-, T-, myeloid, or null cell lines. Isolated normal peripheral blood B and T lymphocytes and monocytes failed to bind B532. The monoclonal antibody did not inhibit in vitro EBV infection nor did it block the killing of EBV-infected targets by cytotoxic T lymphocytes. The cell surface antigen recognized by B532 was shown by immunoprecipitation to have a mol wt of approx 45,000. (Author abstract) (38 Refs)

15. CHARACTERISTICS OF HUMAN EMBRYONIC LUNG CELLS (HEL) TRANSFORMED BY RESTRICTION ENDONUCLEASE (XBA) FRAGMENTED HCMV DNA (MEETING ABSTRACT)

Boldogh I, Huang ES, Gonczol E, Vaczi L
Medical University of Debrecen, Debrecen, Hungary
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The long period before tumors are detected can be a reflection of the capacity for a latent interaction which occurs with HCMV (Human Cytomegaloviruses) under natural conditions. The mechanism in nature by which the normally cytolytic HCMV infection may become a transformation event are not known. It seems that the HCMV induced carcinogenesis may be a multistep process involving an initiator (eg HCMV) and an environmental factor (cocarcinogen). To test this hypothesis, HEL cells were transfected with restriction endonuclease (Xba) cleaved HCMV DNA. The transfection was accomplished by using the calcium phosphate technique. Nineteen and 28 days after transfection cells were treated with a tumor promoting agent 12-O-tetradecanoyl-acetate (TPA). Morphologically altered foci developed 38 +/-6 days after transfection in monolayers of TPA treated and untreated HEL cells. The isolated colonies of morphologically altered cells expressed HCMV specific nuclear antigen(s) and they were positive for HCMV nucleic acids detected by in situ hybridization. From the 47 colonies three independently isolated continuous cell lines were developed and characterized. (no Refs)

16. HUMAN PROTEINS SENSITIVE TO NEOPLASTIC TRANSFORMATION IN CULTURED EPITHELIAL AND FIBROBLAST CELLS.

Bravo R, Celis JE
European Molecular Biology Lab., Postfach 10, 2209 Meyerhofstrasse 1, 6900 Heidelberg, W. Germany
Clin Chem; 28(4,part2):949-954 1982

We resolved the [35S]methionine polypeptides synthesized by normal [lung fibroblasts (WI-38), amnion cells] and transformed [SV40 transformed WI-38, AMA (spontaneously transformed amnion cells)] cultured human cells, using two-dimensional gel electrophoresis under conditions in which about 1,300 polypeptides could be reproducibly separated. These studies demonstrated important changes in the relative proportions of several polypeptides that are present both in normal and transformed cells. Of a total of 400 common polypeptides that we quantitated for each cell type, 53 (22 basic and 31 acidic) varied by 40% or more in both cell pairs. Among these, we have identified vimentin (IEF 26), cyclin (IEF 49), and a tropomyosin-related polypeptide (IEF 52). No new major polypeptide was detected in the transformed cells, at least at the level of resolution currently achieved by this technique. Similar but qualitative studies of [32P]orthophosphate-labeled proteins revealed that, of 250 analyzed, only 7 common phosphoproteins, including phosphovimentin (IEF 26e), varied consistently in both cell pairs. These results strengthen our previous conclusion that transformation results in changes in the relative proportions of polypeptides synthesized in normal and transformed cells rather than in the appearance of new polypeptides in transformed cells. (Author abstract) (28 Refs)

17. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?

Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

Persistence of papova viruses; molecular organization of polyoma virus, simian virus 40 (SV40), and BK virus; transformation by polyoma virus and SV40; and persistence of viral sequences within transformed cells are reviewed. When considering the viral sequences retained within cell transformed polyoma virus and SV40, the main difference is that for maintenance of the transformed state, the entire 'early' region of SV40 appears to be required whereas with polyoma virus such is not the case. Similarities that emerge are those reflecting the presence of viral genomes within transformed cells, tandem arrays of viral sequencés, and a general lack of specificity in the integration sites between viral and host cell DNA. (64 Refs)

18. DETECTION OF JC VIRAL DNA IN BRAIN TUMORS OF JC VIRUS INFECTED MONKEYS (MEETING ABSTRACT)

Miller NR, Wallen WC, London WT
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):689 1982

JC virus is a human papovavirus isolated from the brains of patients with progressive multifocal leukoencephalopathy (PML), a rare demyelinating disease most often seen in immunosuppressed patients. In an attempt to produce an animal model in which to study PML, this laboratory inoculated owl and squirrel monkeys intracranially with JCV. None of the animals developed PML, but over 1/3 of the inoculated animals developed gliomas after a latent period of approximately 2 years. There were no tumors in the uninoculated control animals, strongly suggesting that JCV is involved in tumor initiation and/or development. Molecular hybridization of cloned JCV DNA to restriction endonuclease digested cellular DNA fragments demonstrated the presence of integrated JCV DNA in the gliomas but not in normal tissue of the animals. Analysis of the tumor DNA clearly demonstrated that the viral sequences were JCV, not those of related papovaviruses (BK virus or SV40). The presence of integrated JCV DNA is, therefore, clearly associated with the gliomas in the JCV-inoculated monkeys. In all the tumors examined, there was tandem integration of two or more copies of the viral genome. In all but one, there were unique integration sites, indicating a clonal origin for the tumors. (no Refs)

VIRUS REPLICATION AND EXPRESSION

19. ENHANCING ELEMENTS FOR ACTIVATION OF EUKARYOTIC PROMOTERS.

Yaniv M

Institut Pasteur, 28 rue du Dr Roux, 75724 Paris Cedex 15, France

Nature; 297(5861):17-18 1982

Short viral sequences that stimulate the transcription of coding sequences from their own promoters, termed 'enhancers,' are discussed. Viral enhancers can affect the activity of eukaryotic genes; they are not limited to papovavirus and have been found in retroviruses. The presence of enhancers in retroviruses may explain results that do not fit the simple promotion model of viruses as applied to oncogenesis. Enhancers may play a role in regulating cellular differentiation at the level of tissue- or cell type-specific control of gene expression. (22 Refs)

20. A STUDY OF HLA AND DRW ANTIGENS IN SEVERE RECURRENT HERPES PROGENITALIS (HSV-2) INFECTION.

Ahmed AR, Strom H, Bierman S, Myers-Elliot R, Tiwari P, Terasaki PI

Div. Dermatology, UCLA Sch. Medicine, CHS 52-121, Los Angeles, CA, 90024

J Am Acad Dermatol; 6(5):898-901 1982

HLA-A, HLA-B, HLA-C, and HLA-DR antigen distribution was studied in 93 white men (20-53 yr old, mean age 34 yr) with recurrent herpes progenitalis (RHP) to determine whether specific genetic and immunologic factors regulate the expressivity and predilection to RHP infection. Data are expressed as phenotypic frequency in 558 controls compared with simultaneously typed patients with RHP. The only antigens showing significant frequencies were HLA-A2, HLA-A3, HLA-Bw22, and HLA-Bw51. If probabilities were corrected for the number of antigens tested (39), no antigens showed a significant frequency of less than or equal to 0.05. The results of typing for HLA-DR antigens in 87 patients and 281 controls are presented. The frequency of DRw7 increased significantly in the patient group (p less than or equal to 0.009). This increase was also significant when the p value was multiplied by 6, the number of DR antigens studied in the sample. The relative risk associated with the antigens was 2.1. No statistically increased frequency of HLA-B5 or DRw5 was observed. No increased incidence of HLA-Aw31 or HLA-A1 was observed. Results added significant information to the interaction between the host and the virus that is determined by genetic predisposition. The limitations of the study are that only white men in the Los Angeles area were studied. (25 Refs)

21. HERPESVIRUS GLYCOPROTEIN SYNTHESIS AND INSERTION INTO PLASMA MEMBRANES.

Peake ML, Nystrom P, Pizer LI

(c/o Pizer) Dept. Microbiology and Immunology, Univ. Colorado Health Sciences Center, Denver, CO, 80262

J Virol; 42(2):678-690 1982

In the presence of the antibiotic tunicamycin (TM), glycosylation of herpes simplex virus glycoproteins is inhibited and non-glycosylated polypeptides analogous to the glycoproteins are synthesized. The synthesis of viral proteins and DNA occurs in TM-treated cells. By electron microscopy, nucleocapsids can be observed both in the nucleus and the cytoplasm and TM-treated cells; a small number of enveloped virions were observed on the cell surface. Analyses of the proteins in partially purified virus readily detects viral glycoproteins in the control cells, but neither glycoproteins nor nonglycosylated polypeptide analogs were observed in the virus prepared from TM-treated cells. By labeling the surface of infected cells with 125I, viral glycoproteins were detected as soon as 90 min after infection even when protein synthesis was inhibited with cycloheximide and glycosylation was blocked with TM. Labeling the proteins synthesized in infected cells with [35S]methionine showed that the surface glycoproteins detected in the cycloheximide- and TM-treated cells were not synthesized de novo after infection, but were placed on the cell surface by the infecting virus. Studies with metabolic inhibitors and a temperature-sensitive mutant blocked early in the infectious cycle showed that glycoproteins gA/gB and gD were synthesized soon after infection, but that the synthesis of gC was delayed. Under conditions of infection, in which gC and its precursor pgC are not produced, we have been able to observe the relationships between the glycosylated polypeptides that correspond to pgA/pgB and the nonglycosylated analog made in the presence of TM. (Author abstract) (47 Refs)

22. A NON-X-LINKED SYNDROME WITH SUSCEPTIBILITY TO SEVERE EPSTEIN-BARR VIRUS INFECTIONS.

Fleisher G, Starr S, Koven N, Kamiya H, Douglas SD, Henle W

Div. Infectious Diseases, Children's Hosp. Philadelphia, 34th and Civic Center Blvd., Philadelphia, PA, 19104

J Pediatr; 100(5):727-730 1982

Three siblings developed severe (2) or fatal (1) infectious mononucleosis. This family differed from previously described kindreds with a susceptibility to overwhelming Epstein-Barr virus infections in that: (1) both males and females were affected; (2) they had a history of recurrent bacterial infections; (3) they produced the full spectrum of antibodies to EBV in the expected range of titers; and (4) survivors recovered completely. Two of these youths, but not their parents or an unaffected sibling with mild IM, had a deficiency of natural killer activity that did not respond to preincubation of their peripheral blood mononuclear cells with interferon. NK activity may have an important role in controlling infections with EBV. (Author abstract) (15 Refs)

23. CELLULAR AND EPSTEIN-BARR VIRUS SPECIFIC DNA POLYMERASES IN VIRUS-PRODUCING BURKITT'S LYMPHOMA CELL LINES.

Allaudeen HS, Rani G

Pharmacology Dept., Yale Univ. Sch. Medicine, New Haven, CT, 06510

Nucleic Acids Res; 10(7):2453-2465 1982

We have determined the levels of cellular DNA polymerases and Epstein-Barr virus specific DNA polymerase in three Burkitt's lymphoma cell lines producing varying amounts of EBV, one of which was induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). There was a proportional increase in the level of EBV-DNA polymerase with an increase in the percent of virus-producing cells. However, there was a reciprocal relationship between the levels of EBV-DNA polymerase and DNA polymerase alpha ie, in cell line containing the highest level of EBV-DNA polymerase, activity of DNA polymerase alpha, but not of DNA polymerase beta, was reduced to an insignificantly low level. TPA does not have any direct effect on activities of either EBV-DNA polymerase or DNA polymerase alpha. EBV-DNA polymerases isolated from cells grown with or without TPA are indistinguishable in their properties such as elution position on phosphocellulose column, molecular weight, mono and divalent cation requirements, pH optimum, and other requirements for optimum activity. Addition of crude extracts of cells grown in presence of TPA to the purified DNA polymerase alpha did not inhibit its activity indicating that the observed loss was not due to any specific inhibitor present in TPA treated cells. Raji, a non-producer cell line, did not contain EBV-DNA polymerase. There was no induction of EBV-DNA polymerase when Raji cells were grown in presence of TPA. The phenomenon of reduction in the levels of DNA polymerase alpha in cells induced to produce EBV may represent a mechanism by which the host DNA replication is shut off following virus infection. (Author abstract) (36 Refs)

24. SYNTHESIS OF HUMAN ADENOVIRUS EARLY RNA SPECIES IS SIMILAR IN PRODUCTIVE AND ABORTIVE INFECTIONS OF MONKEY AND HUMAN CELLS.

Anderson KP, Klessig DF

Dept. Cellular, Viral, and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84132

J Virol; 42(2):748-754 1982

Northern (RNA) blot analysis has been used to show that synthesis of early mRNA species is similar in monkey cells productively or abortively infected with human adenovirus. mRNA species from all five major early regions (1A, 1B, 2, 3, 4) are identical in size and comparable in abundance whether isolated from monkey cells infected with adenovirus Type 2 or with the host range mutant Ad2hr400 or coinfected with adenovirus Type 2 plus simian virus 40. The mRNA species isolated from monkey cells are identical in size to those isolated from human cells. Production of virus-associated RNA is also identical in productive and abortive infections of monkey cells. Synthesis of virus-associated RNA is, however, significantly greater in HeLa cells than in CV1 cells at late times after infection regardless of which virus is used in the infection. (Author abstract) (36 Refs)

25. EXPRESSION OF THE GENE ENCODING THE ADENOVIRUS DNA TERMINAL PROTEIN PRECURSOR IN PRODUCTIVELY INFECTED AND TRANSFORMED CELLS.

Binger MH, Flint SJ, Rekosh DM

Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544

J Virol; 42(2):488-501 1982

The major product of in vitro translation of early RNA prepared from H5ts125-infected cells and selected by hybridization to adenoviral DNA fragments spanning the region from 14.7 to 31.5 map units has been shown to be identical to the 87-kilodalton terminal protein precursor. A 72-to 75-kilodalton polypeptide whose mRNA can be selected by DNA from this region and made in the presence of anisomycin was indistinguishable from the 72-kilodalton single-stranded DNA-binding protein encoded by the region from 60.1 to 66.6 map units. The accumulation of cytoplasmic RNA sequences complementary to these l-strand genes under various conditions of infection and in certain lines of transformed cells has been investigated by solution hybridization of cytoplasmic RNA to the separated strands of restriction endonuclease fragments of adenoviral DNA. During the early phase, RNA sequences complementary to the region from 11.6 to 36.7 map units were present at a concentration of 10 to 60 copies per cell, regardless of the nature of the block used to inhibit viral DNA synthesis. By 24 hr after infection in the absence of any such block, sequences complementary to the regions from 11.6 to 18.2 map units (IVa2) and from 18.6 to 36.7 map units (E2B) accumulated to concentrations of 4,800 and 280 copies per cell, respectively. The ratio of cytoplasmic E2A RNA sequences to E2B RNA sequences remained close to 10:1 throughout the time period investigated. Of the transformed cell lines which retained E2B DNA sequences that were examined, only the T2C4 line expressed these sequences in cytoplasmic RNA. The implications of these observations for regulation of expression of the adenoviral early l-strand genes are discussed. (Author abstract) (73 Refs)

26. SITE OF PREMATURE TERMINATION OF LATE TRANSCRIPTION OF SIMIAN VIRUS 40 DNA: ENHANCEMENT BY 5,6-DICHLORO-1-BETA-D-RIBOFURANOSYLBENZIMIDAZOLE.

Skolnik-David H, Hay N, Aloni Y

Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel

Proc Natl Acad Sci USA; 79(9):2743-2747 1982

Sedimentation analysis of pulse-labeled RNA synthesized in nuclei isolated from simian virus 40-infected cells revealed an abundance of short cellular and viral RNAs. The reactive amount of the short chains is increased in nuclei isolated from cells treated with 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB). The short viral RNAs were purified by hybridization to and elution from simian virus 40 DNA on filters, and their sizes were determined by gel electrophoresis. A major band of 93-to 95-nucleotide-long RNA was observed along with additional minor bands. Identical bands were revealed when the viral RNA was purified from nuclei of cells pretreated with DRB. The major band was identified as an aborted transcript of a RNA that initiated at the major initiation site (nucleotide 243). We have found that the DNA region where the RNA stops is A + T rich and is immediately preceded by a G + C-rich region that exhibits dyad symmetry, resembling the termination signal in prokaryotes. These observations show that RNA polymerase II responds to the same termination signal as the prokaryotic enzyme and suggest that a mechanism of attenuation regulates simian virus 40 late transcription. (Author abstract) (47 Refs)

27. INITIATION OF SV40 DNA REPLICATION IN VIVO: LOCATION AND STRUCTURE OF 5' ENDS OF DNA SYNTHESIZED IN THE ORI REGION.

Hay RT, DePamphilis ML

Medical Res. Council Virology Unit, Church St., Glasgow, G11 5JR, Scotland

Cell; 28(4):767-779 1982

Initiation sites for DNA synthesis were located at the resolution of single nucleotides in and about the genetically defined origin of replication (ori) in replicating SV40 DNA purified from virus-infected cells. About 50% of the DNA chains contained an oligoribonucleotide of six to nine residues covalently attached to their 5' ends. Although the RNA-DNA linkage varied, the putative RNA primer began predominantly with rA. The data reveal that initiation of DNA synthesis is promoted at a number of DNA sequences that are asymmetrically arranged with respect to ori: 5' ends of nascent DNA are located at several sites within ori, but only on the strand that also serves as the template for early mRNA, while 5' ends of nascent DNA with the opposite orientation are located only outside ori on its early gene side. This clear transition between discontinuous (initiation sites) and continuous (no initiation sites) DNA synthesis defines the origin of bidirectional replication at nucleotides 5210-5211 and demonstrates that discontinuous synthesis occurs predominantly on the retrograde arms of replication forks. Furthermore, it appears that the first nascent DNA chain is initiated within ori by the same mechanism used to initiate nascent DNA ('Okazaki fragments') throughout the genome. (Author abstract) (63 Refs)

28. DIFFERENT HISTONE FAMILIES IN INTRACELLULAR SV40 NUCLEOPROTEIN COMPLEXES WITH RESPECT TO THE ACETYLATION TURNOVER.

Vesco C, Fantuzzi LF

Institute Cell Biology CNR, Via Romagnosi 18A, 00196 Roma, Italy

Virology; 118(2):389-400 1982

The turnover of normal and butyrate-induced acetylation in the histones complexed with intracellular SV40 DNA was analyzed in infected CV-1 cells. The analysis concerned the two principal structures containing the intracellular SV40 chromatin: the 75 S complexes and the provirions. It was found that, while the normal acetylation in the 75 S chromatin turns over a lower rate than that of the host-cell chromatin, the hyperacetylation induced by butyrate turns over a rate very close to that of cell chromatin. This distinguishes two families of 75 S histones, presumably corresponding to nucleosomes with different accessibility to histone-modifying enzymes. A third type of turnover is shown by the provirion histones, in which the normal acetylation occurs at a low rate but is highly conserved. The response to butyrate in these structures is either absent or similar to that of the 75 S histones. In the chromatin of the late SV40 mutant tsB11, histone hyperacetylation does not occur when infection proceeds at the restrictive temperature for the coat-protein assembly. The hyperacetylation of histones which characterizes the morphogenesis of SV40 appears to be an assembly-dependent process, starting in the 75 S chromatin and building up mainly in the provirions. (Author abstract) (38 Refs)

29. EMERGENCE OF SIMIAN VIRUS 40 VARIANTS DURING SERIAL PASSAGE OF PLAQUE ISOLATES.

Norkin LC, Tirell SM

Dept. Microbiology, Univ. Massachusetts, Amherst, MA, 01003

J Virol; 42(2):730-733 1982

Three serial passage series of simian virus 40 (SV40) in CV-1 cells were initiated by infection directly from the same wild-type plaque isolate, three series were initiated by infection with another plaque isolate, and two series were initiated with each of two other plaque isolates. Aberrant SV40 genomes were not detected in any of the passage series until after the fifth undiluted passage, and each series generated a different array of variant genomes. The results show that the variants were not present in the original plaque isolates but, instead, were randomly generated during subsequent high-input multiplicity passage. Although many of the aberrant viral genomes in each passage series contained reiterations of the SV40 origin of replication and some also contained host cell sequences, there was no indication that SV40 is predisposed toward generating any particular variant. (Author abstract) (18 Refs)

30. INTRACELLULAR TRANSPORT OF SV40 LARGE TUMOR ANTIGEN: A MUTATION WHICH ABOLISHES MIGRATION TO THE NUCLEUS DOES NOT PREVENT ASSOCIATION WITH THE CELL SURFACE.

Lanford RE, Butel JS

(c/o Butel) Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX, 77030

Virology; 119(1):169-184 1982

The cT mutation of PARA, an SV40-adenovirus 7 hybrid virus, abolishes the transport of SV40 T-antigen (T-ag) to the nucleus and results in the accumulation of T-ag in the cytoplasm of infected and transformed cells. The effect of the cT mutation on the association of T-ag with the cell surface was examined in PARA(cT)-infected monkey cells. Surface-associated T-ag was detected by immunofluorescence, lactoperoxidase-catalyzed cell-surface iodination, and cellular fractionation. Surface-associated T-ag was more readily labeled by cell-surface iodination with PARA(cT)-infected cells than with SV40 and wild-type PARA [PARA(nT)]-infected cells. Control experiments eliminated the possibility that the enhanced detection of T-ag in PARA(cT)-infected cells was due to the labeling of intracellular T-ag by lactoperoxidase or to T-ag leaking from dead cells and adhering to the cell surface. The elevated level of surface-associated T-ag in PARA(cT)-infected cells was confirmed by metabolic labeling and cellular fractionation, indicating that the increased iodination of surface-associated T-ag was due to a greater number of T-ag polypeptides on the surface rather than a greater exposure of tyrosine residues. Pulse-chase experiments demonstrated that the elevated level of surface-associated T-ag in PARA(cT)-infected cells was not due to a prolonged stability of surface-associated T-ag. The cT mutation provides a useful tool for studies of mechanisms governing intracellular protein transport. (Author abstract) (47 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

31. EXPRESSION OF CELLULAR HOMOLOGUES OF RETROVIRAL ONC GENES IN HUMAN HEMATOPOIETIC CELLS.

Westin EH, Wong-Staal F, Gelmann EP, Favera RD, Papas TS, Lautenberger JA, Eva A, Reddy EP, Tronick SR, Aaronson SA, Gallo RC
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(8,part1):2490-2494 1982

Total cellular poly(A)-enriched RNA from a variety of fresh human leukemic blood cells and hematopoietic cell lines was analyzed for homology with molecularly cloned DNA probes containing the ONC sequence of Abelson murine leukemia virus (Ab-MuLV), Harvey murine sarcoma virus (Ha-MuSV), simian sarcoma virus (SSV), and avian myelocytomatosis virus strain MC29. Results with the fresh blood cells paralleled those obtained with the cell lines. With Ab-MuLV and Ha-MuSV, multiple RNA bands were visualized in all cell types examined without significant variation in the relative intensities of the bands. When SSV was used as the probe, expression of related onc sequences was absent in all of the hematopoietic cell types examined except for one neoplastic T-cell line (HUT 102), which produces the human T-cell leukemia (lymphoma) retrovirus HTLV. In this cell line, a single band (4.2 kilobases) was observed. With MC29 as the probe, a single band of 2.7 kilobases was visualized in all cell types examined with only a one- to two-fold variation in intensity of hybridization. An exception was the promyelocytic cell line, HL60, which expressed approximately 10-fold more MC29-related onc sequences. With induction of differentiation of HL60 with either dimethyl sulfoxide or retinoic acid, a marked diminution in the amount of the MC29-related, but not the Ab-MuLV-related, onc message was observed. (Author abstract) (62 Refs)

32. MECHANISM OF RESISTANCE TO ARA-C IN A MUTANT HERPESVIRUS (MEETING ABSTRACT)

Schnipper LE, Crumpacker CS, Antman K, Kufe D
Harvard Medical School, Boston, MA, 02215
Proc Am Assoc Cancer Res; 23:868 1982

Adenine arabinoside (ara-A) and cytosine arabinoside (ara-C) are effective inhibitors of cellular and Herpes Simplex virus type 1 (HSV-1) DNA synthesis. A mutant of HSV-1 (Ara-Ar) selected in ara-A, and resistant to both ara-A and ara-C has been employed to study mechanisms of resistance to arabinofuranosyl derivatives. Incorporation of ara-C into wild type HSV-1 (KOS) and HSV-1 (ara-Ar) DNA was monitored by isopycnic centrifugation of viral DNA with 3H-ara-C and 32P 6-20 hours post-infection of Vero cells. 32P labelling serves as a measure of relative rates of DNA synthesis. At a concentration of 5 x 10-7M ara-C, the ratio of 3H-ara-C to 32P incorporation into DNA was 0.1 for HSV-1 (ara-Ar) compared to 1.0 for HSV-1 (KOS). When compared to KOS, DNA synthesis with Ara-Ar was less inhibited by ara-C up to a concentration of 5 x 10-6M and was associated with formation of less ara-C DNA. Above 5 x 10-6M there is linear incorporation of 3H-ara-C into mutant viral DNA, and inhibition of DNA synthesis comparable to that in HSV-1 (KOS). High pressure liquid chromatographic analysis of purified viral DNA digested to 3'-nucleotides demonstrates that ara-C is incorporated into internucleotide linkage in both wild type and mutant viruses, between 10(-7)-10-5M. At high concentrations (greater than 10-5M), a greater proportion of ara-C residues are present at the chain terminus. The extent of ara-C incorporation into DNA correlates with inhibition of plaque formation such that HSV-1 (ara-Ar) is insensitive to concentrations less than 5 x 10-6M, whereas HSV-1 (KOS) plaque formation is inhibited in linear fashion between 10(-7)-10-4M. HSV-1 (ara-Ar) resistance to ara-C is overcome above concentrations of 5 x 10-6M. Resistance to ara-C is closely related to exclusion of this analog from viral DNA, however, the precise enzymatic mechanism is not yet understood. (no Refs)

33. DETAILED STRUCTURAL ANALYSIS OF TWO SPLICED HSV-1 IMMEDIATE-EARLY MRNAS.

Rixon FJ, Clements JB
Inst. Virology, Univ. Glasgow, Glasgow G11 5JR, Scotland
Nucleic Acids Res; 10(7):2241-2256 1982

The structures of two HSV-1 immediate-early mRNAs have been determined by nuclease-digestion procedures using 5' and 3' end-labeled DNA probes. These mRNAs, which map across the junctions between the short unique (US) and short repeat (IRS and TRS) genome regions, have common 5' portions located in IRS and TRS. The 3' portions, which extend into opposite ends of US, are unique. The DNA sequence encoding the common 5' portions largely comprises a 247 base pair (bp) leader region and a single intron of variable size. The variation in intron length is due to different copy numbers of a 22 bp tandem reiteration. A small proportion of the mRNA population is unspliced, but otherwise is identical to the more abundant spliced species. (Author abstract) (38 Refs)

34. AN OLIGORIBONUCLEOTIDE POLYMERASE FROM SV40-INFECTED CELLS WITH PROPERTIES OF A PRIMASE.

Kaufmann G, Falk HH
Biochemistry Dept., Weizmann Inst. Science, Rehovot 76100, Israel
Nucleic Acids Res; 10(7):2309-2321 1982

A transient decaribonucleotide (iRNA) is covalently linked to nascent eukaryotic DNA chains at their 5' end. Searching for the putative iRNA polymerase (primase), we detected in extracts from SV40-infected cells a DNA-dependent incorporation of UMP residues from UTP into free and DNA linked deca- or similarly sized ribonucleotides. Denatured salmon sperm DNA served as the standard template in this reaction. SV40 FIII DNA was also an effective template, SV40 FII DNA was ineffective while FI yielded mainly free decaribonucleotides. The incorporation depended on the other rNTPs and was resistant to high concentrations of alpha-amanitin and rifamycin AF/013, drugs inhibitory to RNA polymerases I, II and III. The results implicate the decaribonucleotide polymerase in the priming of nascent DNA chains and suggest that the unique size of iRNA is encoded within its primase. (Author abstract) (27 Refs)

35. AN SV40 DELETION MUTANT ACCUMULATES LATE TRANSCRIPTS IN A PARANUCLEAR EXTRACT.

Campos R, Villarreal LP
(c/o Villarreal) Dept. Microbiology and Immunology, Sch. Medicine, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Virology; 119(1):1-11 1982

We have constructed a deletion in the SV40 late region which has lost the sequences between nucleotides 226 and 656. This deletion has lost most of utilized 5' ends, leaders, all of the intervening sequence and body acceptor site for late 19 S mRNA. We show that the transcripts made by this deletion are concentrated in a paranuclear extract relative to other subcellular fractions. Furthermore, the late transcripts of the helper virus used to grow this mutant are also concentrated in the paranuclear extract. This observation leads us to speculate that these mutant transcripts may poison the RNA transport process. (Author abstract) (33 Refs)

36. DEPENDENCE OF TUMOR-FORMING CAPACITIES OF CELLS TRANSFORMED BY RECOMBINANTS BETWEEN ADENOVIRUS TYPES 5 AND 12 ON EXPRESSION OF EARLY REGION 1.

Shiroki K, Maruyama K, Saito I, Fukui Y, Yazaki K, Shimojo H
(c/o Shimojo) Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, 108, Japan
J Virol; 42(2):708-718 1982

Recombinants between an adenovirus Type 5 (Ad5) deletion mutant and the Ad12 DNA fragment containing early Region 1 (E1) were isolated from cells cotransfected with the EcoRI-C fragments of Ad12DNA and Ad5 dl312 (deletion in E1A) DNA (rcA) and from cells cotransfected with the SalI-C fragment of Ad12 DNA and Ad5 dl312 DNA (rcB). No recombinant was isolated from cells cotransfected with Ad5 dl313 (deletion in E1B) DNA and restriction fragments of Ad12 DNA. Both rcA and rcB are defective and able to replicate in human embryo kidney (HEK) and KB cells with complementation by dl312. Both rcA and rcB formed Ad12 T antigen g, but not T antigen f, in infected HEK and KB cells. In rcA- and rcB-infected cells, Ad5 E1B and Ad12 E1A genes are transcribed. Heteroduplex and size analysis of rcA-1 or rcB-1 DNA fragments hybridized with Ad12 DNA revealed that rcA-1 DNA has a deletion between 5 and 15 map units with an insertion of a portion of Ad12 DNA (10%) and that rcB-1 DNA has a deletion between 70 and 80 map units with an insertion of a portion of Ad12 DNA (10%). The transformed cell lines, RCAY and RCBY, were established after infection of rat 3Y1 cells with rcA and rcB, respectively. Both Ad5 and Ad12 DNA sequences are contained in these cells. In RCAY cells, Ad12 T antigen g is detected, but Ad12 T antigen f is not. In RCBY cells, both Ad12 T antigens g and f are detected. Only the Ad12 E1A gene is transcribed in RCAY cells, whereas Ad5 E1B, Ad12 E1A, and Ad12 E1B genes are transcribed in RCBY cells. In soft-agar cultures, RCBY cells form large colonies, whereas RCAY cells form only tiny colonies. RCBY cells form tumors as efficiently as 12WY cells in transplanted rats. RCAY cells formed tumors inefficiently. Ad5-transformed 5WY cells do not form tumors. These observations indicate that the efficient tumor formation by RCBY cells is dependent on the expression of the Ad12 E1A and E1B genes, whereas the inefficient tumor formation by RCAY cells is due to the expression of only the Ad12 E1A gene. (Author abstract) (28 Refs)

37. ADENOVIRAL PROTEIN-PRIMED INITIATION OF DNA CHAINS IN VITRO.

Ikeda JE, Enomoto T, Hurwitz J
Dept. Molecular Genetics, Inst. Plant Virus Res., Tsukuba Science-City, Yatabe, Ibaraki 305, Japan
Proc Natl Acad Sci USA; 79(8,part1):2442-2446 1982

The initiation of DNA chains by the 80-kilodalton form of the adenovirus terminal protein has been studied. This protein, which can be covalently linked to dCMP, is isolated complexed to a 140-kilodalton protein possessing DNA polymerase activity. In the presence of adenovirus DNA-protein, the formation of the 80-kilodalton protein-dCMP complex requires the addition of ATP and nuclear extract from uninfected cells in addition to Mg++ and dCTP. When single-stranded DNA is used in place of the adenovirus DNA-protein, the formation of the 80-kilodalton protein-dCMP complex occurs in the absence of ATP and nuclear extract. In the presence of the four dNTPs, the complex yields DNA chains of various sizes between 100 and 300 nucleotides. The products formed with bacteriophage phiX174 single-stranded circular DNA as the template are site specific, predominantly derived from the sequences between nucleotides 2363 and 2977 and between nucleotides 3760 and 4206. These small DNA chains are blocked at their 5' ends with the 80-kilodalton protein but possess free 3'-OH ends that are susceptible to degradation by exonuclease III and can be elongated to replicative form II products with DNA polymerase I of Escherichia coli or eukaryotic DNA polymerase beta preparations. A protein priming model explaining the different requirements for initiation with adenovirus DNA-protein and with phiX174 DNA is presented. (Author abstract) (20 Refs)

38. POLYPEPTIDES ENCODED BY TRANSFORMING REGION E1B OF HUMAN ADENOVIRUS 2: IMMUNOPRECIPITATION FROM TRANSFORMED AND INFECTED CELLS AND CELL-FREE TRANSLATION OF E1B-SPECIFIC MRNA.

Matsuo T, Wold WS, Hashimoto S, Rankin A, Symington J, Green M
(c/o Green) Inst. Molecular Virology, St. Louis Univ. Medical Center, 3681 Park Ave., St. Louis, MO, 63110
Virology; 118(2):456-465 1982

We have identified polypeptides specific to region E1b (map position [mp] 4.6-11.2) of adenovirus 2 (Ad2) that are synthesized in six lines of Ad-transformed rat or human cells (F17, F4, T2C4, 8617, 5RK clone I, 293), and in Ad2 early infected KB cells. [35S]Methionine-labeled polypeptides were immunoprecipitated using antisera against F17 cells, an Ad2-transformed rat cell line that retains only E1. To determine whether they are viral coded, these polypeptides were compared by tryptic peptide mapping with polypeptides translated in vitro from Ela-specific mRNA (mp 1.3-4.5) and E1b-specific mRNA. Polypeptides of 19,000 daltons (19K), 20K, and 53K were immunoprecipitated from Ad2 early infected KB cells. The 19K, 20K, and 53K could be translated from E1b-specific mRNA and thus are coded by E1b. The 19K was precipitated from all transformed cell lines, the 20K was immunoprecipitated from F4, 8617, and T2C4 cells, and the 53K was immunoprecipitated from F4, 8617, T2C4, and 293 cells. These results suggest that the 19K, and perhaps the 20K and 53K, may be important in adenovirus-induced cell transformation. The 20K and 53K share methionine-containing tryptic peptides with each other, but not with the 19K. These results, together with the Ad2 E1b DNA sequence suggest that 19K is translated in a different reading frame from 53K and 20K. (Author abstract) (39 Refs)

39. MUTATION AFFECTING LATE GENE EXPRESSION IN POLYOMA VIRUS MAPS IN THE LATE REGION.

Thomas EK, Hare JD
(c/o Hare) Dept. Microbiology, Univ. Rochester Medical Center, Rochester, NY, 14642
J Virol; 42(2):719-724 1982

A mutation in polyoma virus strain 3049 which results in the overproduction of capsid proteins has been mapped to the late region of the genome between the HindIII site at 45.0 map units and the BamHI site at 58.6 map units. This region contains the coding sequence for VP3 and a portion of VP2 but does not include the late promoters or the coding sequence for the late leaders. The possible role of VP2 or VP3 in the regulation of genetic expression in polyoma virus is discussed. (Author abstract) (29 Refs)

40. ENCAPSIDATION AND EXPRESSION OF THE HERPES THYMIDINE KINASE GENE IN POLYOMA VIRUS.

Dinces NB, Milman G
(c/o Milman) Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
J Virol; 42(2):691-699 1982

A recombinant DNA of 5,150 base pairs was prepared containing the intact early region of polyoma virus, including the viral origin of replication and the structural sequences of the herpes simplex virus Type 1 thymidine kinase gene. Although no thymidine kinase activity was detected when herpes structural sequences alone were transfected into cells, activity was produced when the structural gene followed the polyoma early region. The recombinant DNA was encapsidated into polyoma virions when cotransfected into mouse 3T6 cells with helper DNA from an early polyoma virus mutant. Herpes thymidine kinase activity was detected by a rapid in situ autoradiographic assay in which $[^{125}I]$iododeoxycytidine was utilized as a substrate for the viral but not the cellular enzyme. (Author abstract) (15 Refs)

41. POLYOMA VIRAL MIDDLE T-ANTIGEN IS REQUIRED FOR TRANSFORMATION.

Mes AM, Hassel JA
(c/o Hassel) Dept. Microbiology and Immunology, McGill Univ., Montreal, Quebec H3A 2B4, Canada
J Virol; 42(2):621-629 1982

To determine whether small or middle T-antigen (or both) of polyoma virus is required for transformation, we constructed mutants of recombinant plasmids which bear the viral oncogene and measured the capacity of these mutants to transform rat cells in culture. Insertion and deletion mutations in sequences encoding small and middle T-antigens (79.7, 81.3, and 82.9 map units) rendered the DNA incapable of causing transformation by the focus assay. Similar mutations in sequences that encoded middle but not small T-antigen (89.7, 92.1, and 96.5 map units) generally abolished the transforming activity of the DNA. However, two mutants (pPdl1-4 and pPdl2-7) that carried deletions of 92.1 map units retained the capacity to transform cells; pPdl1-4 did so at frequencies equal to those of the parental plasmid, whereas pPdl2-7 transformed at 10% the frequency of its antecedent. From these studies we conclude that small T-antigen alone is insufficient to cause transformation and that middle T-antigen is required for transformation, either in combination with small T-antigen or by itself. (Author abstract) (43 Refs)

42. TWO DEFECTIVE DNAS OF HUMAN POLYOMAVIRUS JC ADAPTED TO GROWTH IN HUMAN EMBRYONIC KIDNEY CELLS.

Yoshiike K, Miyamura T, Chan HW, Takemoto KK
Dept. Enteroviruses, Natl. Inst. Health, Shinagawa-ku, Tokyo 141, Japan
J Virol; 42(2):395-401 1982

Human polyomavirus JC (JCV) adapted to growth in human embryonic kidney (HEK) cells contains two or more species of shorter-length viral DNA even after two cycles of plaque purification in HEK cells. We have molecularly cloned JCV DNA from one plaque isolate and determined the physical map of its DNA. Using gel electrophoresis and electron microscopy, we found that the cloned DNA consisted of two classes of JCV DNA. One class of DNA had a deletion of 30% (between 0.7 and 1.0 map units from the EcoRI site) and an insertion of 1% at the same site in the late region. The other had a deletion of 35% (0.18 to 0.53 map units) and an insertion of 12% at the same site in the early region of the JCV genome. Both DNAs had added sequences near the origin of DNA replication. From their structure, the two DNAs appear to complement each other. These results indicate that the HEK-adapted JCV may be replicating by complementation between two defective mutants. (Author abstract) (25 Refs)

IMMUNOLOGICAL STUDIES

43. SERO-EPIDEMIOLOGIC STUDIES ASSOCIATE THE HUMAN T-CELL LEUKEMIA-LYMPHOMA VIRUS (HTLV) WITH ADULT MALIGNANCY OF MATURE T-CELLS (MEETING ABSTRACT)

Robert-Guroff M, Kalyanaraman VS, Sliski A, Blattner W, Catovsky D, Sarngadharan MG, Gallo RC
Litton Bionetics, Inc., Kensington, MD, 20895
Fed Proc; 41(3):689 1982

HTLV, a unique human retrovirus (RNA tumor virus), was isolated from cells of patients with lymphomas and leukemias of mature T-cells. Surveys of sera for antibodies to HTLV have shown HTLV to be rarely associated with such diseases in the US, but strongly linked to Japanese adult T-cell leukemia (ATL), lymphosarcoma T-cell leukemia (LCL), and peripheral T-cell lymphoma. LCL is a malignancy of mature T-cells seen in some Caribbeans. ATL is a similar disease clustered geographically in Southwest Japan. Sera of 19 of 22 ATL patients and 3 of 3 LCL patients had antibodies to HTLV p24 and p19 as determined by radioimmunoprecipitation of p24 or by competition radioimmunoassay with a monoclonal anti-p19. Among sera of relatives of sero-positive patients, 20% were also positive, supporting the infectious nature of HTLV. Other normal donors lacked antibodies to HTLV, except for some healthy Japanese in the ATL endemic area, suggesting widespread viral exposure. Sera of children in the US with leukemias, lymphomas, and solid tumors were negative, as were sera from numerous adults with various neoplasias. While HTLV is thus not prevalent in this country, it may play a role in the etiology of mature T-cell neoplasias in other geographic locales. (no Refs)

44. A NOVEL LEUKAEMIA-ASSOCIATED ANTIGEN RECOGNIZED BY A BABOON ANTISERUM (MEETING ABSTRACT)

Guibout C, Dore JF, Archimbaud E, Dubouch P
Hopital Paul Brousse, Villejuif, France
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The immune serum of baboon immunized with fresh cells from a patient with E- SmIg- ALL (acute lymphocytic leukemia) was absorbed with pooled HRBC and cells from an autologous B cell line established by EBV (Epstein Barr Virus) infection of the patient's remission lymphocytes. The absorbed serum does not react with normal lymphocytes, nor with 10 lymphoblastoid cell lines and an endometrial carcinoma cell line expressing Ia-like antigen. In a microcytotoxicity assay, it kills 2/3 T-ALL lines, 4/4 non T, non B-ALL lines, 0/2 myeloid lines. It reacts also with fresh cells from ALL (T and nT, nB), some AML, cALLAg- lymphomas and few CLL (chronic lymphocytic leukemia). Further absorption of the antiserum with Molt-4 line abolishes its reactivity with T cell lines and T-ALL cells; absorption with Daudi line absorbs out its reactivity with Daudi and KM-3 lines without modifying the activity on nT, nB cell lines or fresh cells. Absorption with NALM-1 line (a pre-B line) absorbs out most of the antiserum reactivity, and the antiserum does not react anymore with nT, nB-ALL lines nor fresh cells. Radioimmunoprecipitation assays using 125I-labelled NALM-1 membranes, followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis showed that the antiserum precipitates 3 proteins with apparent molecular weight of 25, 175 and 260K. The 25K protein seems to be the one associated with nT, nB-ALL and is shared with normal human platelets which can absorb out the reactivity of the antiserum with nT, nB-ALL. None of these proteins can be associated with Daudi or cALL antigens. (no Refs)

45. STUDIES ON ONCOVIRUS-SPECIFIC IMMUNOLOGICAL MARKERS IN PATIENTS WITH LEUKAEMIA AND PRELEUKAEMIC DISORDERS (MEETING ABSTRACT)

Toth FD, Vaczi L, Kiss J, Rethy A, Szabo B, Kiss A, Rak K
Institute of Microbiology and 2nd Department of Medicine, University Medical School, 4012 Debrecen, Hungary
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Extracts from peripheral leukocytes of patients with chronic myeloid leukemia (CML) were examined for antigens related to the p30 polypeptide of baboon endogenous virus (BaEV) and gibbon ape leukemia virus (GaLV) by competitive RIA (radioimmunoassay). Leukocytes of patients with the quiescent phase of CML proved to be negative or contained only the p30 of BaEV. In the accelerated phase or blastoid crisis of CML an antigen related to the p30 of GaLV could be detected. In 5 of 6 patients, acceleration or blastoid crisis was preceded by expression of GaLV p30. Immune response to cell surface antigens related to the gp70 of BaEV and GaLV was studied by 51Cr-release technique. Highly intensive cytotoxic activity to autologous leukocytes mediated by lymphocytes or antibodies could be demonstrated in the majority of patients with the quiescent phase of CML or preleukemic disorders. In patients with acute leukemias immune response was found very rarely. (no Refs)

46. ANTIBODIES CROSS-REACTING WITH GROSS VIRUS DETECTED IN HUMAN ACUTE LEUKEMIA AND HODGKIN'S LYMPHOMA (MEETING ABSTRACT)

Segal-Eiras A, Dosne-Pasqualini C
Departamento de Patologia, Universidad Nacional de La Plata, Buenos Aires, Argentina
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

By immunofluorescence and immunoperoxidase tests, using AKR thymus and lymphoma cells as targets, it has been possible to detect antibodies in the sera of 62% of 218 patients with acute lymphoblastic leukemia, 65% of 23 with acute myeloid leukemia and 702% of 26 with Hodgkin disease. Seventy-nine normal controls gave negative results. The positive sera could be absorbed with the respective target cells and with autologous human leukemia cells but not with BALB thymocytes, AKR Kidney cells or normal lymphocytes. Swiss embryo fibroblasts infected with AKR leukemic extracts, used as target cells gave a positive IF response when incubated with human sera 'positive' on AKR target, while normal human sera or non-infected fibroblasts gave negative results. The IF reaction could be blocked with anti-RadLV serum, used because of its similarity with anti-Gross serum. It can be concluded that in the sera of most patients with acute leukemia and Hodgkin disease, antibodies are present, which cross-react with antigens related to Gross virus. (no Refs)

47. USE OF SEPHAROSE BEAD IMMUNOFLUORESCENCE ASSAY FOR COMPARISON OF THE TYPE D RETROVIRUSES MPMV AND PMFV.

Micheel B, Uckert W, Denner J, Fiebech H, Wunderlich V
Dept. Experimental Clinical Immunology, Central Inst. Cancer Res., Acad. Sciences GDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(4):275-282 1982

Experiments using the Sepharose bead immunofluorescence assay (SBIFA) for comparing Mason-Pfizer monkey virus (MPMV) and a type D retrovirus isolated from a continuous human fibroblast line (PMFV) are reported. MPMV p27 related antigens were demonstrated in experiments using sandwich SBIFA and in those using competition SBIFA. The p15 of PMFV contained antigenic determinants not present in MPMV. Both viruses reacted almost identically in the PMFV p27-specific assay, while there was no reaction of MPMV and a distinct reaction of PMFV in the PMFV p15-specific assay. (19 Refs)

48. EBV-IGA AND NEW HETEROPHILE ANTIBODY TESTS IN DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS.

Evans AS, Niederman JC
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
Am J Clin Pathol; 77(5):555-560 1982

An evaluation has been made of the EBV-IgA tests and the immune adherence hemagglutination assay (IAHA) as compared with standard diagnostic procedures in 119 serial sera from 22 clinical and 113 sera from 42 subclinical cases of EBV infectious mononucleosis. EBV-IgA antibody was demonstrable in 86.4% of patients using EB3 cells as antigen and in 68.2% with P3/HRIK cells. For heterophile antibody the IAHA test was more sensitive, gave higher titers, and was positive longer than the standard absorbed horse or sheep RBC tests in both clinical and subclinical EBV infections. (Author abstract) (16 Refs)

49. A HETEROANTISERUM AGAINST AMERICAN BURKITT'S LYMPHOMA (BL) (MEETING ABSTRACT)

Magrath IT, Parsons RG
Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:1039 1982

We have raised a goat antiserum (B75) against purified membrane from an American BL cell line and examined its spectrum of reactivity after extensive absorption with either 5 African BL cell lines or 6 Epstein Barr Virus-transformed cord blood lymphocyte (CBL) cell lines. Both methods of absorption yielded antisera with identical specificities. Eleven of 12 EBV genome-negative cell lines derived from American BL (6) and undifferentiated non-BL (6) reacted with B75 using indirect immunofluorescence. Three of 4 EBV genome-positive American undifferentiated lymphomas were also positive, but none of 13 CBL lines or 8 non-tumor lymphoblastoid cell lines reacted with B75. Two of 7 African BL cell lines reacted positively. These 2 lines also secreted small amounts of IgM, whereas none of the 5 negative lines did so. B75 did react with blast cells derived from common acute lymphoblastic leukemia (ALL) but not with blast cells from T-cell ALL or lymphoblastic lymphoma. B75 reactivity persists after incubation of cells with proteolytic enzymes and we have so far been unable to immunoprecipitate a protein from cell lysates with B75. These data indicate that BL cells express one or more antigens not present on other lymphoid cell lines of normal and neoplastic origin. These data are consistent with the hypothesis that American-BL and undifferentiated lymphoma are the neoplastic counterparts of cell types early in the B-cell pathway, probably immediately after the pre-B cell stage, and before the normal counterpart of African BL. (no Refs)

50. BLA: A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN DEFINED BY A MONOCLONAL ANTIBODY (MEETING ABSTRACT)

Lipinski M, Wiels J, Fellous M, Tursz T
Institut Gustave-Roussy, 94800 Villejuif, France
Fed Proc; 41(3):726 1982

A rat monoclonal IgM antibody (38-13) has been raised against Daudi cells, derived from a Burkitt lymphoma (BL). This antibody defined an antigen, referred to as BLA, specifically expressed on Burkitt tumor cells, whether they contain the Epstein-Barr virus (EBV) genome or not. BLA is not detected on EBV-positive lymphoblastoid cell lines, normal or mitogen activated lymphocytes, or fresh malignant cells from patients affected with various non-BL lymphoproliferative disorders. Therefore, 38-13 recognizes a BL-associated antigen clearly not related to EBV. Biochemical analysis indicates that BLA is a hydrophobic glycoconjugate: the antigen resists proteolytic treatments; no specific protein is detected by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) analysis after precipitation of radio-labeled BL membranes with 38-13; the antibody is specifically absorbed by a chloroform-methanol extract of BL cells; immunofluorescence staining for BLA is inhibited in the presence of D-galactose, N-acetylneuraminic acid and N-acetyl D-galactosamine. Since it displays an apparent specificity for BL cells, the 38-13 monoclonal antibody could represent a valuable tool for diagnosis and specific immunotherapy of BL. (no Refs)

51. P105, AN EBV-INDUCED TARGET OF THE IMMUNE RESPONSE (MEETING ABSTRACT)

Jones W, Casareale D, Reisert PS, Spiro RC, Sairenji T, Humphreys RE
University of Massachusetts Medical School, Worcester, MA, 01605
Fed Proc; 41(3):803 1982

In order to characterize EBV-induced targets of the immune response, a 00 dalton glycoprotein prominently recognized in immunoprecipitates of, Burkitt's lymphoma patients' sera with P3HR-1 EBV-superinfected Raji cells (S-Raji), was analyzed through the use of a specific heteroantiserum. Synthesis of p105 was restricted to EBV-superinfection and was not blocked with phosphonoacetic acid, indicating p105 to be an 'early' viral antigen. An external exposure of p105 on the cell surface was indicated by its glycosylation with radiolabeled sugars, by antibody binding in a radioimmunoassay with living cells and by membrane immunofluorescence. Although anti-p105 serum did not neutralize P3HR-1 virus (but bound to P3HR-1 cell membranes), it mediated antibody-dependent cellular cytotoxicity (ADCC) to EBV-superinfected Raji and to control Raji cells but not to several EBV genome-negative cell lines. We conclude that p105 is an EBV-induced, external, glycosylated, early membrane antigen to which EBV-infected patients generate a substantial antibody response. These antibodies do not neutralize infectious virus but might mediate ADCC to, or otherwise affect, infected cells early in the virus cycle. (no Refs)

52. EPSTEIN-BARR-VIRUS-SPECIFIC T-CELL MEMORY IN RENAL-ALLOGRAFT RECIPIENTS UNDER LONG-TERM IMMUNOSUPPRESSION.

Gaston JS, Rickinson AB, Epstein MA
(c/o Epstein)Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England
Lancet; 1(8278):923-925 1982

The level of long-term responsiveness of cytotoxic T cells to Epstein-Barr (EB) virus has been measured in peripheral-blood mononuclear-cell cultures from symptom-free renal-allograft recipients under conventional immunosuppression. Eight of 22 patients showed a profoundly impaired responsiveness when compared with healthy control donors. The allograft recipients as a group showed raised antibody titers to EB-virus capsid and early antigens, but within the group there was no clear relation between these antibody titers and the level of EB-virus-specific cytotoxic-T-cell function. These findings are particularly relevant to the pathogenesis of the malignant lymphomas to which renal-allograft recipients are unusually susceptible, in view of the evidence implicating EB virus. (Author abstract) (28 Refs)

53. MONOCLONAL ANTIBODIES TO EPSTEIN-BARR VIRUS-INDUCED, TRANSFORMATION-ASSOCIATED CELL SURFACE ANTIGENS: BINDING PATTERNS AND EFFECT UPON VIRUS-SPECIFIC T-CELL CYTOTOXICITY.

Rowe M, Hildreth JE, Rickinson AB, Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Int J Cancer; 29(4):373-381 1982

Spleen cells from mice immunized with Epstein-Barr virus-transformed lymphoblastoid cells (EB-LCL) were used to generate monoclonal antibodies to cell surface antigens associated with the EB virus-transformed state. Radioimmune and immunofluorescence binding assays identified two antibodies, MHM6 and AC2, which reacted consistently with all EB-LCL tested, with a subpopulation of cells in some but not all EB virus genome-positive Burkitt lymphoma lines, but with none of a range of EB virus genome-negative cell lines of lymphoma or leukemia origin. While MHM6 appeared to bind an EB virus-related antigen, AC2 bound some other cell surface antigen which was also found on a small subpopulation of cells in lymphocyte cultures stimulated with phytohemagglutinin or with pokeweed mitogen. MHM6 and AC2 recognized single polypeptides with apparent mol wt of 45 kd and 80 kd respectively as shown by sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE) analysis of 125I-labeled cell surface polypeptides immunoprecipitated with these antibodies. These polypeptides were induced on experimentally-infected B cells within 24 hr of the expression of the EB virus nuclear antigen, EBNA, at a time known to coincide with the appearance of the lymphocyte-detected membrane antigen, LYDMA. However, saturating concentrations of MHM6 and of AC2 were unable to protect EB-LCL target cells from lysis by LYDMA-specific cytotoxic T cells in a chromium-release assay. (Author abstract) (50 Refs)

54. HEPATITIS B VIRUS AND PRIMARY LIVER CANCER: DEMONSTRATION OF A CYTOPLASMIC TUMOR ANTIGEN IN THE TRANSFORMED HEPATOCYTE.

Romet-Lemonne JL, Barin F, Goudeau A, Maupas P
Institut de Virologie de Tours, Facultes de Medecine et de Pharmacie, 2bis, boulevard Tonnelle, 37000 Tours, France
C R Acad Sci [III] (Paris); 294(1):9-14 1982

The presence of tumor antigen was studied in human hepatoma cell line PLC/PRF/5 by indirect immunofluorescence and immunoperoxidase assay using antisera from 14 Senegalese patients with primary hepatocellular carcinomas. Ten of the 14 sera were HBs Ag-positive, 4/10 also HBe Ag-positive, 3/14 anti-HBsd antibody-positive and 1/14 anti-HBc antibody-positive. Twenty-two sera without hepatitis B virus markers from African Blood donors and from cancer patients were used as controls. Tumor antigen (HBV/T) was found in the cytoplasm of the human hepatoma cells. The same antigen was also detected in primary hepatocellular carcinoma tissues. The data obtained with serum and tissue controls indicate that the HBV/T Ag-anti-HBV/T system seems to be associated with the transformation of hepatocytes by hepatitis B virus. (15 Refs) (In FRE)

55. CLINICAL SIGNIFICANCE OF THE DETERMINATION OF HBSAG, ANTI-HBS AND ANTI-HBC IN VIRAL HEPATITIS AND PRIMARY LIVER CANCER.

Min X, Han Y, Wang M, Chen Z
Dept. Infectious Diseases, Nanjing Medical Coll., Nanjing, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):106 1981

Results of HBsAg, Anti-HBs and Anti-HBc determination are described for 139 cases of various types of viral hepatitis and 16 cases or primary liver cancer. There were 99 males and 56 females, 7-75 yr old. The positive rates of HBsAg, Anti-HBs and Anti-HBc in patients with viral hepatitis were 56.8%, 33.8% and 45.3%, respectively, while those in patients with liver cancer were 56.4%, 25.0%, and 62.5%, respectively. Hepatitis B was closely related to primary liver cancer. (no Refs) (In CHI)

56. CELLULAR PROTEINS REACTIVE WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST SIMIAN VIRUS 40 T-ANTIGEN.

Crawford L, Leppard K, Lane D, Harlow E
Dept. Molecular Virology, Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
J Virol; 42(2):612-620 1982

Several recently isolated monoclonal antibodies which reacted with simian virus 40 T antigens also reacted with proteins found in uninfected and untransformed cells. The proteins were different from each other, PAb419 reacting with a 35,000-mol-wt protein, PAb427 reacting with a 75,000-mol wt phosphoprotein, PAb405 reacting with a 150,000-mol-wt phosphoprotein, and PAb204 reacting with a 68,000-mol wt protein. It is suggested that although some of these cross-reactions may be fortuitous, they may, as an alternative, reflect similarities of shape and perhaps function between domains of the viral T antigen and the relevant host proteins. (Author abstract) (29 Refs)

57. NASOPHARYNGEAL CARCINOMA IN CENTRAL PENNSYLVANIA.

Bushey MJ, Strauss M, Conner B
Div. Otolaryngology, Milton S. Hershey Medical Center, Hershey, PA
Trans Pa Acad Ophthalmol Otolaryngol; 35(1):55-59 1982

Twelve cases of nasopharyngeal carcinoma in patients 17-80 yr old (av 45.4 yr old) are discussed. The most common presenting symptoms were neck mass and otologic symptoms. Lesions were epidermoid carcinomas (4), poorly-differentiated carcinomas (4), undifferentiated carcinomas (3), and lymphoepithelioma (1). Three patients exhibited cranial nerve involvement; of those patients tested, most had elevated titers of viral capsid antigen (9/11) and early antigen (9/10). All patients underwent radiation therapy; survival was 50%, with a 24-mo av follow-up. (33 Refs)

VIRAL STUDIES IN HUMAN CANCER

58. ASYMPTOMATIC TYPE C VIRUS CARRIERS IN THE FAMILY OF AN ADULT T CELL LEUKEMIA PATIENT.

Miyoshi I, Taguchi H, Fujishita M, Niiya K, Kitagawa T, Ohtsuki Y, Akagi T
Dept. Medicine, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan
Gan; 73(2):339-340 1982

Serologic and virologic studies were performed in 14 members of the family of a 49-yr-old male patient with adult T cell leukemia (ATL). The patient and family lived in Kochi, an area where the incidence of ATL appears to be relatively high. ATL antigens (ATLA) and Type C virus particles were detected in short-term cultures of peripheral lymphocytes from 4/5 family members who were ATLA antibody positive. The five ATLA antibody positive family members were all asymptomatic and hematologically normal except for one member, in whom a persistent leukocytosis with several percent abnormal lymphocytes had been observed for two yr. It was not yet determined whether vertical or horizontal infection was involved in the virus transmission in this family. (5 Refs)

59. A RETROVIRUS ASSOCIATED WITH HUMAN ADULT T CELL LEUKEMIA: IN VITRO ACTIVATION.

Hinuma Y, Gotoh Y, Sugamura K, Nagata K, Goto T, Nakai M, Kamada N, Matsumoto T, Kinoshita K
Inst. Viral Res., Kyoto Univ., Shogoin Kawahara-machi, Sakyo-ku, Kyoto 606, Japan
Gan; 73(2):341-344 1982

Presence of adult T cell leukemia antigen (ATLA) was studied in the mononuclear cell fractions of peripheral blood derived from 11 patients (9 men, 2 women; 48-83 yr old) with adult T cell leukemia (ATL), from a 54-yr-old man with mycosis fungoides (MF), and from 8 healthy adults (6 men, 2 women; 21-44 yr old). The mononuclear cell fractions were cultured in the presence and/or absence of interleukin-2 (IL-2) or T cell growth factor. Some of the fractions were also examined with electron microscopy for virus particles. ATLA positive cells were not detected in any of the cell preparations examined prior to culturing. However, ATLA-bearing cells were observed in the cultures from 6/11 ATL patients and 1/2 ATLA antibody-positive healthy subjects. No ATLA-bearing cells were detected in cultures of one patient with MF and six ATLA antibody-negative healthy subjects. High percentages of ATLA positive cells were found 2-3 days after starting cultures without IL-2; the ATLA were located in the cytoplasm of rather small leukemic cells and were often aggregated. The ATLA-bearing cells in cultures supplemented with IL-2 for a greater than 2 wk were large and often multinuclear with blastoid morphology. Presence of Type C virus particles was observed with electron microscopy in ATL-derived cultures with a high percentage of ATLA positive cells. The results showed that (1) peripheral blood cells of many patients with ATL contain sufficient information for ATLA or ATL virus (ATLV) formation in a repressed form, and suggest that (2) ATLA is associated with ATLV and (3) ATLV is present not only in ATL patients but also in anti-ATLA positive healthy individuals. (6 Refs)

60. KAPOSI'S SARCOMA. A CASE REPORT AND COMMENTARY ON ETIOLOGICAL FACTORS.

Reymond JL, Beani J, Stoebner P, Amblard P
Service de Dermatologie, Centre Hospitalier Regional de Grenoble, B.P. 217 X, F 38043 Grenoble, France
Lyon Med; 247(5):201-204 1982

A 71-yr-old man from Naples, Italy, presented with nodular formations extremely indicative of Kaposi's disease. Biopsy followed by histological examination failed to confirm the clinical diagnosis. When further nodular lesions developed on the knees and toes of the patient, they were also biopsied. A final diagnosis of Kaposi's sarcoma (KS) was made. The etiological factors implicated in KS are cancer, viruses, malfunctioning of the immune response, and ethnic and geographic factors. It is generally agreed that the malignant process is plurifocal rather than metastatic and that the course of the malignancy varies from one patient to another. (no Refs) (In FRE)

61. KAPOSI'S SARCOMA IN HOMOSEXUALS.

Thivolet J
Clinique Dermatologique, Pavillon R, Hopital E. Herriot, F 69374 Lyon, France
Lyon Med; 247(5):189-190 1982

Kaposi's sarcoma has been diagnosed in increased frequency among the homosexual male population in New York City and San Francisco. The typical form of the disease affects the extremities and 70-90% of the affected patients are men. The new form which affects the head and the body as well as the arms has been found only in men. The clinical signs are disseminated papules and nodules with frequent ganglionic involvement. The disease has a rapid deterioration with 20% mortality before 2 yr. Cytomegalovirus and immunodeficiencies have been implicated in the disease. (8 Refs) (In FRE)

62. COLIC CARCINOMA AND BASAL CELL EPITHELIOMA ELEVEN YEARS AFTER KAPOSI SARCOMA WITH SPLENIC AND CUTANEOUS INVOLVEMENT.

de Plunkett TL, Pieron R, Dreyfus F, Meyniel D
Service de Medecine Interne, Hopital Tenon, 4, rue de la Chine, 75020 Paris, France
Sem Hop Paris; 58(17):1027-1030 1982

A case of Kaposi sarcoma (KS) with cutaneous and splenic involvement is reported. Carcinoma of the left colon and basal cell epithelioma arose 11 years after KS. Genetic, viral, and immunologic factors which may promote initiation and development of Kaposi sarcoma are reviewed. The responsibility of immunodeficiency, whether resulting from therapy or from other causes, in carcinogenesis is discussed. Prolonged survival may be seen after KS. Another primary malignant disease (lymphoma or solid tumor) may arise. The authors suggest that the risk of immunologic disorders, occurring spontaneously or induced by therapy, should be considered specifically for each patient with KS. (Author abstract) (14 Refs) (In FRE)

63. CYTOMEGALOVIRUS DNA, RNA AND SPECIFIC ANTIGEN(S) IN TUMOR BIOPSIES OF KAPOSI'S SARCOMA (MEETING ABSTRACT)

Giraldo G, Boldogh I, Beth E, Huang ES

Instituto Nazional dei Tumori, Naples, Italy

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

A number of observations indicate that cytomegalovirus (CMV) may play an important role in induction of Kaposi's sarcoma (KS). According to our recent results CMV-DNA homologous sequences, CMV specific RNA as well as antigens in tumor biopsies of KS were present, determined by nucleic acid hybridization techniques and ACIF test. Three of ten cellular DNAs, extracted from KS biopsies were shown to contain CMV-DNA homologous sequences in an amount of 0.7-1 viral genom equivalent per diploid cells. In five out of ten 5 um thin frozen sections of tumor biopsies were positive by in situ hybridization representing the presence of virus specific RNA. The CMV specific antigens were localized in the nuclei of cells of tumor sections. This antigen(s) might represent the immediately product of existing viral DNA. In contrast we could not detect any HSV-2 or EBV specific macromolecules (DNA, RNA, viral antigen) in tumor biopsies of KS. (1 Ref)

64. CLINICAL AND LABORATORY FEATURES OF KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN (MEETING ABSTRACT)

Kris M, Safai B, Myskowski P, Koziner B, Urmacher C, Gold J, Armstrong D, Pinsky C, Krown S, Ochoa M, Sherlock P

Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

Proc Am Soc Clin Oncol; 1:C-700 1982

A cluster of Kaposi's Sarcoma (KS) cases has been observed among young homosexual men in the New York City area. Ten patients (pts), all with the onset of symptoms after 12/78, have been seen. THe median age was 38 years (range 32-55); 9 were white and 1 was an American black. Initial sites of disease were skin (8) and oral mucosa (2). Lymphadenopathy was seen in 7 pts and hepatosplenomegaly in 1 on initial examination. One pt had Pneumocystis carinii pneumonia at diagnosis. Gastrointestinal involvement was documented in 5 of 7 pts completely evaluated by either endoscopy or necropsy. Cytomegalovirus (CMV) titers were greater than 1:32 in 9 pts; 1 was anticomplementary. One pt had a 4-fold rise in CMV titer during his illness. Epstein-Barr viral capsid antigen titers, measured by the immunofluorescent antibody technique, were greater than 1:160 in 9 pts tested. CMV was cultured from the urine of 2 of 7 pts. Oral cultures grew Candida albicans in 3 pts. Antibody to hepatitis B was noted in all 5 tested pts. Serum immunoglobulins G, A, and M were normal or elevated in all 6 pts tested. Significantly lower ratios of T-helper (OKT4+) to T-suppressor (OKT8+) cells were noted in KS pts when compared to normal controls using anti-T-cell monoclonal antibodies. Two of the 10 pts died 10 and 16 months after histologic diagnosis despite treatment with chemotherapy. No other pts have received chemotherapy to date. (no Refs)

65. DISSEMINATED INFECTION DUE TO MYCOBACTERIUM AVIUM-INTRACELLULARE IN A HOMOSEXUAL MAN WITH KAPOSI'S SARCOMA.

Fainstein V, Bolivar R, Mavligit G, Rios A, Luna M
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
J Infect Dis; 145(4):586 1982

A case of Kaposi's sarcoma of the skin and scalp that did not respond to antibacterial or anticancer drug therapy is described. The 36-yr-old patient had pneumonia due to Pneumocystis carinii combined with elevated cytomegalovirus (CMV) titer; disseminated mycobacterial infection was another manifestation of severe immunodeficiency. CMV may trigger immunodeficiency and lead to infections due to P. carinii, Candida, mycobacteria, or other organisms. (3 Refs)

66. KAPOSI'S SARCOMA: WHY A 'HOMOSEXUAL DISEASE'?

Groopman JE, Gottlieb MS
Div. Hematology-Oncology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA
Hosp Pract; 17(5):64F-64G,64J,64N,64O,64R,64T 1982

Epidemiology, pathogenesis, classification, and therapy of Kaposi's sarcoma (KS) are reviewed. KS is intimately linked with cytomegalovirus infection in genetically and environmentally diverse hosts. The current epidemic of KS in homosexuals in the United States is one manifestation of a new, acquired immunodeficiency syndrome. Understanding the relationship between homosexuality, viral infection, immune status, and these neoplasms may contribute to understanding the basis of oncogenesis in KS. (43 Refs)

67. OCULAR DISORDERS ASSOCIATED WITH A NEW SEVERE ACQUIRED CELLULAR IMMUNODEFICIENCY SYNDROME.

Holland GN, Gottlieb MS, Yee RD, Schanker HM, Pettit TH
(c/o Pettit), Jules Stein Eye Inst., Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Am J Ophthalmol; 93(4):393-402 1982

Among the prominent features of a newly described acquired cellular immunodeficiency syndrome that affects previously healthy male homosexuals are multiple opportunistic infections and Kaposi's sarcoma. Immunosuppression induced by cytomegalovirus infection may play a major role in the pathogenesis of this disorder. We have performed ophthalmic examinations on seven such patients and found ocular abnormalities in all cases. Six patients were examined during the course of their illness and one patient at autopsy only. Each patient had several cotton-wool spots in the affected eye. Other ocular findings included cytomegalovirus retinitis, severe retinal periphlebitis, and conjunctival Kaposi's sarcoma (1 case each). (Author abstract) (33 Refs)

68. IMMUNOSUPPRESSION SYNDROME IN HOMOSEXUAL MEN. AN EPIDEMIOLOGICAL INVESTIGATION FROM THE CANCER RESEARCH INSTITUTE IN ARHUS.

Biggar RJ, Melbye M, Ebbesen P, Kerzel Andersen H, Vestergaard BF
NCI, Bethesda, MD
Ugeskr Laeger; 144(11):777-780 1982

A sudden increase in the incidence of immunosuppression syndrome with clinically highly malignant Kaposi's sarcoma and recurrent infections in homosexual men in the United States suggests repeated infections with cytomegalovirus. The sniffing of amyl nitrite, was found to be mutagenic in Ames' test, and possible to be a pathogenetic factor. An epidemiological study of 300 homosexual men (16-57-yr-old) in Arhus and Copenhagen revealed that 1/3-1/2 of the subjects used nitrites. Cytomegalovirus in sperm was found in 12% of all cases, ie, somewhat more frequently than in a historical control. (26 Refs) (In DAN)

69. INCREASED FREQUENCY OF HLA-DR5 IN MYCOSIS FUNGOIDES AND KAPOSI'S SARCOMA (MEETING ABSTRACT)

Safai B, Pollack MS, Myskowski L, Dupont B
Sloan-Kettering Institute for Cancer Research, New York, NY, 10021
Fed Proc; 41(3):414 1982

Mycosis Fungoides (MF) is a cutaneous T-cell lymphoma while Kaposi's Sarcoma (KS) is a multicentric neoplasm which often has its primary manifestation in the skin. Although the exact mechanism for initiation of either disease is still unknown, a viral mechanism has been suggested in both cases. Specifically, retroviruses have been associated with some tumor cell lines of MF, and cytomegaloviruses have been associated with KS. In order to investigate the possible role of HLA-associated variations in genetic susceptibility, 64 patients with histologically documented MF and 32 patients with histologically documented KS were typed for HLA-A,B,C antigens. Most of these patients were also typed for HLA-DR antigens. A significant increase in DR5 was the only statistically significant deviation in HLA antigen frequencies in either group (50% in MF and 60% in KS in comparison with 20% in controls). The increase in DR5 was especially striking in the subgroup of KS patients with the particularly aggressive form of KS recently described in young homosexual males. HLA-DR5 has also been associated with scleroderma and juvenile rheumatoid arthritis. Immunologic alterations are involved in the pathogenesis of both, but viral infection may also be a factor. The associations of MF and KS with DR5 thus suggest that some individuals with the DR5 antigen may be at higher genetic risk for virally initiated neoplastic diseases, possibly through an HLA-linked effect in the immune system. (no Refs)

70. KAPOSI'S SARCOMA (KS) IN LYMPH NODES OF A PATIENT WITH CYTOMEGALOVIRUS (CMV) VIREMIA (MEETING ABSTRACT)

Gyorkey F, Sinkovics JG, Luchi RJ, Small SD, Craig P, Rossen R, Gyorkey P, Melnick JL
Veterans Administration Medical Center and Baylor College of Medicine, Houston, TX, 77211
Proc Am Assoc Cancer Res; 23:1106 1982

A 34 yr old homosexual man developed fever, lymphadenopathy and hepatosplenomegaly. He was a long term user of phenytoin. Lymph node pathology showed KS. Vascular endothelial cells, hepatocytes and lymphocytes contained an abundance of cytoplasmic tubuloreticular structures identical with those described by us in lupus and in interferon-treated human lymphoblasts by Rich. Pneumocystis carinii was found by lung biopsy. Giardia lamblia was present in his intestines. CMV was isolated from urine, liver and lung, and also identified by electron microscopy in the biopsy and autopsy tissues. Hypoglobulinemia and depressed cell-mediated immunity were documented. Postmortem, Cryptococcus species was found in some lymph modes in addition to KS. (2 Refs)

71. IMMUNOSUPPRESSION IN A HOMOSEXUAL MAN WITH KAPOSI'S SARCOMA.

Rasmussen EO, Cooper KD, Kang K, White CR, Regan DH, Hanifin JM
(c/o Hanifin) Dept. Dermatology, Oregon Health Sciences Univ., 3181 S.W. Sam Jackson Park Road, Portland, OR, 97201
J Am Acad Dermatol; 6(5):870-879 1982

The case of a 34-yr-old homosexual man with Kaposi's sarcoma, as well as cutaneous anergy and in vitro evidence of depressed cell-mediated immunity, is described. Cytomegalovirus was isolated from urine and semen. Immunosuppression in this patient and possibly other homosexual men appears to be mediated by abnormalities in the immunoregulatory T lymphocytes. (34 Refs)

72. MALIGNANT COURSE OF KAPOSI'S SARCOMA IN HOMOSEXUALS: NEW FINDINGS ON IMMUNE STATUS.

Steigleder GK, Sterry W
Zeitschrift fur Hautkrankheiten, Koln, W. Germany
Z Hautkr; 57(9):627-628 1982

A sharp increase in the incidence of Kaposi's sarcoma (KS) has been reported among homosexual men who live in or have visited New York or several other cities in the United States. The increase is accompanied by a similar increase in opportunistic infections. The cause is evidently infection by cytomegalovirus. Use of so-called 'recreational' drugs is apparently also a related factor. The increase in KS may be the result of a defect in the immune system. (no Refs) (In GER)

73. ACQUIRED IMMUNOLOGICAL DEFECT IN HOMOSEXUAL MEN. A NEW CLINICAL PICTURE.

Gerstoft J, Malchow-Moller A, Bygbjerg ICh, Dickmeiss E, Halberg P, Jacobsen M, Jensen K, Nielsen JO, Thomsen HK, Sondergaard J, Lorenzen I
Afsnit for Reumatologi/immunologi, Kobenhavns kommunes Hvidovre hospital, DK-2650 Hvidovre, Denmark
Ugeskr Laeger; 144(11):771-776 1982

Acquired immune defect was diagnosed in four homosexual men, including two sexual partners, during a 1-yr period. Febrility, loss of weight, generalized lymphadenopathy and opportunistic infections were found. Kaposi's sarcoma was diagnosed in 2/4 patients. Cytomegalovirus infection was established in 2/4 cases. Three of the four patients sniffed nitrites. (30 Refs) (In DAN)

74. LYMPHADENITIS CAUSED BY EPSTEIN BARR VIRUS AND BY CYTOMEGALOVIRUS.

Cuppini R
Ospedale Civile, 61029 Urbino, Italy
Minerva Med; 73(15):923-928 1982

Lymphadenitis caused by Epstein Barr virus or by cytomegalovirus were reviewed including clinical symptoms, differential diagnosis, epidemiology, relationship with neoplastic diseases (Hodgkin's disease, Burkitt's lymphoma), infectious mononucleosis, and treatment with metisoprinol. (50 Refs) (In ITA)

75. ETIOLOGY OF MOUTH AND LIP TUMORS.

Zabezhinskii MA, Godorozha PD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982

Literature data on the etiology of mouth and lip cancers are reviewed. Pathogenesis of mouth neoplasms is associated with the exposure to various chemical, physical, and biological carcinogenic factors alone or in combination with the modifying factors. The increased incidence of mouth cancer can be caused by smoking, tobacco chewing, exposure to polycyclic aromatic hydrocarbons, alcohol consumption, and exposure to pesticides. Physical carcinogens include UV, x rays, and sunlight. Experimental data indicate that herpes virus and polyoma virus can induce adenomas and adenocarcinomas of mouth mucosa. Poor hygiene of the mouth can increase the risk of development of mouth cancer. Chronic irritation of the mouth mucosa was shown to enhance penetration of carcinogens into mucosa and to stimulate cell proliferation. Bacterial flora of the oral cavity was shown to contribute to the metabolism of chemical carcinogens. Deficiency of vitamins A and B led to development of precancerous conditions of the mouth mucosa. (74 Refs) (In RUS)

76. DETECTION AND QUANTITATION OF IMMUNOGLOBULINS ASSOCIATED WITH TUMORS OF THE HUMAN ORAL CAVITY.

Pillai S, Sasidharan VK, Balaram P, Vivekanandan S, Vasudevan DM
Regional Cancer Center, Medical Coll. Campus, Trivandrum 695 011, India
Indian J Cancer; 19(1):44-46 1982

IgA and IgM were quantitated by radial immunodiffusion on agar plates containing IgA, IgG and IgM antisera. Alpha amylase activity was measured in tissue extracts to eliminate saliva contamination which contains high amounts of IgA. IgA and IgG were found only in tumor extracts, supporting the concept of tumor associated antibodies. Potassium chloride was used to extract membrane integral proteins or membrane bound proteins and no IgG was quantitated in these extracts. This suggests that IgG may be present in the cytoplasmic portion of the cell extract or present on the surface of tumor cells attached to other membrane proteins. The role of herpes simplex virus in pathogenesis of oral cancer is discussed; cells transformed by DNA viruses carry virus specific antigens. Immunoglobulins in tumor extracts might also be a reaction to these virus specific antigens. (19 Refs)

77. COMBATING POSTMENOPAUSAL GYNECOLOGIC MALIGNANCY.

Roseushein NB, Rotmensch J
Dept. Gynecology and Obstetrics, Johns Hopkins Hosp., Baltimore, MD
Geriatrics; 37(5):107-110,115-116 1982

Risk, histogenesis, pattern of spread, detection and management of cervical, endometrial, and ovarian cancer are discussed. Cervical cancer (CC) may be thought of as a venereal disease because of its relationship to sexual activity. There is increasing evidence that herpes simplex virus Type 2 is associated with CC. Preinvasive lesions can be easily eradicated; due to screening with cervical cytology, risk of death from CC is half of what was 20 yr ago. Annual screening is recommended. Screening in endometrial cancer, being controversial and of unproven usefulness, should be restricted to the 'high risk patient'. For all stages of disease, surgery plus radiation provides the highest cure rate and the lowest incidence of recurrence. Ovarian cancer does not respond to surgery alone. Even at an early stage, adjuvant immunotherapy, chemotherapy, or radiotherapy are important components of treatment. Staging of the three gynecologic cancers is presented in tabular form. (12 Refs)

78. POLYMORPHISM OF NUCLEAR INCLUSIONS IN CARCINOMA OF THE CERVIX UTERI.

Georgescu L, Dragan M, Teodorescu M, Diosi P, Petrascu-Stefanovici O, Raica M
Dept. Morphopathology, Timisoara Medical Inst., Timisoara, Romania
Morphol Embryol (Bucur); 28(1):31-34 1982

Frequency, polymorphism and ultrastructural characteristics of the nuclear inclusion bodies in the surgical specimens of 20 patients with epidermoid carcinoma of the uterine cervix are reported. Electron microscopy revealed inclusion bodies of three distinct types: nuclear bodies of types I and II according to the classification of Bouteille et al, inclusion bodies of cytoplasmic origin, and particles consisting of chromatic material. Type I nuclear bodies have a round form and a concentric fibrillar structure; these bodies are less electron-dense than chromatin and numbered 1-3 per nucleus. The Type II bodies in addition had a central accumulation of electron-dense granules. The intracytoplasmic inclusions were found in the nuclei of both epithelial and stromal cells and had the appearance of euchromatin and with the presence of nucleoli. These bodies usually contained cytoplasmic organelles (mitochondria). Particles of chromatic material were limited by a clear halo suggesting a process of maturation of viral cores, these inclusions appeared singly or in small groups in the nucleoplasm. These particles had an exo- or centronucleus location, frequently coexisting with the Type II nuclear inclusion bodies. The particles with chromatic material were encountered especially in cervical cancer with a low grade of differentiation. There appears to be a direct relation between the frequency of the chromatic particles and raised antiherpetic antibodies to herpesvirus, as determined by serological study of the patients' sera. (8 Refs)

79. HUMAN PAPILLOMAVIRUS AND NEOPLASIA OF THE GENITAL TRACT IN IMMUNODEFICIENT WOMEN (MEETING ABSTRACT)

Shokri-Tabibzadeh S, Koss LG, Molnar J, Romney S
Department of Pathology, Montefiore Hospital and Medical Center, Albert Einstein College of, Medicine Bronx, NY
Acta Cytol (Baltimore); 25(6):716 1981

The possible role of human condyloma viruses (HCV) in the genesis of squamous cell carcinoma of the genital tract of women was studied in four immunodeficient patients. Three of the patients had a treated Hodgkin's disease and one had a dermatologic disorder, perhaps akin to epidermodysplasia verruciformis. All four patients developed treatment-resistant condylomata acuminata of the vulva and adjacent areas. One of the patients developed carcinoma in situ (CIS) of the cervix and of the labia majora, five and eight years, respectively, after the appearance of condylomata. Another patient developed CIS of the vulva, vagina, uterine cervix and perineum three years after the appearance of condylomata. This last patient developed multifocal, invasive carcinomas of both labia majora, vagina and perineum eight years later. The presence of HCV was documented by electron microscopy in squamous epithelium of the cervix and vagina and in cells derived therefrom in all four patients as well as in CIS and in the superficial component of invasive carcinoma of the third and fourth patients. The persistence of codylomata in these patients, with the progression of these patients, with the progression of the disease toward atypical epithelial change to invasive carcinoma and the presence of HCV in the neoplastic squamous epithelium of the genital tract of these immune-suppressed women, adds yet another link of evidence to the possible association of HCV with neoplastic events. (no Refs)

80. GENITAL INFECTION WITH HERPES SIMPLEX VIRUS.

Griffiths BL
Dept. Nursing, Univ. Alabama, Birmingham, AL
Nurs Times; 78(13):545-548 1982

The history and pathobiology of genital infection with herpes simplex virus (HSV) are discussed. HSV infection is most often accompanied by a history of sexual contact within the past 5-12 days. Recurrent disease is estimated to develop in 60-80% of patients who acquire the disease. HSV infection, while it is associated with an increased incidence of cervical cancer, should not be presented to the patient as a premalignant condition. Women with genital HSV should be encouraged to undergo regular cervical examination (every 6-18 mo). (4 Refs)

81. BURKITT'S DISEASE.

Rain JD
Faculte de medecine, BP V. 166, Abidjan, Ivory Coast
Rev Prat; 32(14):979-981 1982

Discovery, description, clarification, classification, and further developments in knowledge of Burkitt's disease are discussed. Burkitt's lymphoma exists in certain well-defined locations in Africa, where temperature and elevation conditions are favorable for proliferation of the Epstein Barr virus. The disease strikes children 3-9 yr old, and in 77% of cases the tumor is localized in the maxillofacial region. The disease is highly responsive to chemotherapy, particularly cyclophosphamide. Another form of European and American Burkitt's lymphoma exists but is considerably different in etiology and clinical course from the African lymphoma. (no Refs) (In FRE)

82. CURRENT STATUS OF CLINICAL INVESTIGATION ON HEPATITIS, LIVER CIRRHOSIS AND HEPATIC CARCINOMA IN CHINA.

Lin Z
Zhongshan Hosp., Shanghai First Medical Coll., Shanghai, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):79-81 1981

Recent progress in the etiology, diagnostic techniques and treatments is reviewed for hepatitis, liver cirrhosis and liver cancer. The roles of hepatitis B virus, hepatitis B surface antigen, alpha-fetoproteins and numerous enzymes useful in diagnosis are specially discussed. Other topics covered include new diagnostic instrumentation, such as B-mode ultrasonography, scintigraphy, computed tomography and fiber optics. (no Refs) (In CHI)

83. CARRIER STATUS IN HEPATITIS B: A MODERN SCOURGE WITH HOPE.

Iber FL
Univ. Maryland Hosp., Batimore, MD
JAMA; 247(16):2275-2276 1982

The importance of 'carriers' of hepatitis B is discussed. The prevalence of hepatitis B surface antigen (HBsAg) carriers in the general population of the United States is estimated to be 0.2-0.5%. The majority of these patients are entirely asymptomatic, yet the carrier at times represents a clear health hazard to his contacts. The HBsAg carrier is at clear risk of liver disease and hepatocellular carcinoma (HCC). Approx 15-20% of asymptomatic carriers have significant chronic liver disease. At least one half of all patients in whom HCC develops have associated markers of hepatitis B virus. (2 Refs)

84. THE EVOLUTION, IMPLICATIONS, AND APPLICATIONS OF THE HEPATITIS B VACCINE.

Alter HJ
NIH, Bethesda, MD
JAMA; 247(16):2272-2275 1982

One aspect of hepatitis B vaccine is that it might serve indirectly as the first cancer vaccine because of the possible relationship between hepatitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC). Evidence for causality is summarized. The global distribution of hepatitis B surface antigen (HBsAg) carriers and HCC are almost identical. (14 Refs)

85. SIGNIFICANT PROGRESS IN DERMATOLOGIC RESEARCH SINCE 1977.

Lapiere CM
Dept. Dermatology, Univ. Liege, B-4020 Liege, Belgium
J Am Acad Dermatol; 6(2):200-208 1982

Recent dermatologic research (1977-1981) of significance for cancer research includes: the identification of the Langerhans cells and partial elucidation of their role in cell-mediated immunity; the typing of mononuclear cells; the identification of T-lymphocyte growth factors; the association of defined subtypes of human papovavirus with neoplastic transformation; continuing research on melanogenesis and its control by polypeptides; the functions of specific proteins of the keratinocytes; the roles of membrane receptors, growth factors, and intracellular enzymes in the control of epidermal cell proliferation and differentiation; and phototherapy/photochemotherapy of cancer. (129 Refs)

86. HISTOLOGICAL CHANGES IDENTICAL TO THOSE OF CONDYLOMATOUS LESIONS FOUND IN ESOPHAGEAL SQUAMOUS CELL CARCINOMAS.

Syrjanen KJ
Dept. Pathology, Univ. Kuopio, POB 138, SF-70101 Kuopio 10, Finland
Arch Geschwulstforsch; 52(4):283-292 1982

Sixty esophageal specimens obtained from patients subjected to diagnostic endoscopy or surgery for esophageal malignancy were studied to obtain additional information about the supposed role of human papilloma virus (HPV) in human carcinogenesis. The frequencies of the histological parameters suggestive of HPV involvement in the esophageal epithelium associated with squamous cell carcinomas are summarized. The most frequent finding was single cell dyskeratosis, followed by acanthosis, dyskeratotic superficial cells, and multinucleation. (48 Refs)

87. FANCONI'S ANEMIA. TUMOR-LIKE WARTS, HYPERPIGMENTATION ASSOCIATED WITH DERANGED KERATINOCYTES, AND DEPRESSED CELL-MEDIATED IMMUNITY.

Johansson E, Niemi KM, Siimes M, Pyrhonen S
Dept. Dermatology, Helsinki Univ. Central Hosp., Helsinki, Finland
Arch Dermatol; 118(4):249-252 1982

A 27-yr-old man had had Fanconi's anemia (FA) for 20 yr. The patient had pancytopenia, retarded growth, hypogonadism, and chromosomal aberrations. He had freckle-like and darker pigmented macules scattered on his chest, shoulders, upper part of the back, and hips, with interspersed, hypopigmented areas. Biopsy specimens taken from both the hyperpigmented and hypopigmented spots showed a derangement of keratinocytes and nuclear abnormalities, more notable on sun-exposed skin sites. The patient also had numerous tumor-like, recalcitrant, viral warts. Immunologic studies showed normal humoral immunity, but there was evidence of depressed cell-mediated immunity. We speculate that the chromosomal aberrations, the depressed cell-mediated immunity, and the increased frequency of malignant neoplasms known to occur in patients with FA also reflect changes related to an increased susceptibility to viral infections. (Author abstract) (33 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

88. ANTIVIRAL EFFECTS OF DEOXYPODOPHYLLOTOXIN ON HSV-INFECTED AMNION CELL CULTURES.

Markkanen T, Makinen ML, Miettinen J, Laijoki T, Maunuksela E, Hietanen T, Lehto I, Himanen P
Clinical Res. Lab., Univ. Turku, SF-20520 Turku 52, Finland
Drug Exp Clin Res; 8(1):27-34 1982

The effect of deoxypodophyllotoxin (DPT) on normal and herpes simplex-1 virus (HSV)-infected human amnion cell cultures was investigated. DPT sharply decreased the incorporation of thymidine, and moderately increased the incorporation of uridine and methionine in both normal and infected cells. The DPT-treated infected cultures showed no viral cytopathogenic effect. When DPT was removed by washing, incorporation of thymidine increased back to normal levels. DPT inhibited the proliferation of HSV, and did not exhibit virucidal activity. (14 Refs)

89. EPSTEIN-BARR VIRUS-LYMPHOID CELL INTERACTIONS. III. EFFECT OF CONCANAVALIN A AND SACCHARIDES ON EPSTEIN-BARR VIRUS PENETRATION.

Khelifa R, Menezes J
(c/o Menzes) Lab. Immunovirology Pediatric Res. Center, Univ. Montreal, Ste-Justine Hosp., Montreal, Quebec H3T 1C5, Canada
J Virol; 42(2):402-410 1982

To study some aspects of Epstein-Barr virus (EBV) penetration into target cells, the effect of concanavalin A (ConA) and various saccharides on virus infectivity and cell susceptibility to EBV infection was examined. ConA treatment of the target cells, EBV, or EBV-cell complexes was found to inhibit virus antigen expression. Several control experiments with alpha-D-methyl-mannoside elution of ConA, removal of nonfused EBV particles from the cell surface by trypsin treatment, and addition of ConA at different times postinfection were performed to define the site of ConA action on EBV infection. ConA appeared to have a dual action: (i) it inhibited EBV binding to virus receptors, and (ii) it blocked the penetration of receptor-bound virus into target cells at a trypsin-sensitive stage, thus indicating that ConA prevented the fusion of viral envelope with the target cell membrane. A high sucrose concentration (0.25 M), known to inhibit cell membrane movements, was also found to block EBV penetration at a trypsin-sensitive stage, thus suggesting the implication of cell membrane movements and underlying activities (or both) in viral envelope fusion. Lower concentrations of various monosaccharides (0.12 M) did not influence EBV infection. Under conditions of ConA treatment that did not influence EBV infectivity and target cells susceptibility, ConA was able to mediate virus binding to EBV receptor-negative cell lines, but no virus antigens were expressed in these cells. These observations reinforced the idea that the mere attachment of EBV to lymphoid cells is not sufficient to lead to infection. In light of the present and previously published data, we postulate the existence of a specific cellular mechanism that allows the penetration of EBV into the target (B) lymphocyte. (Author abstract) (37 Refs)

90. ANTIVIRAL EFFECTS OF INTERFERON ON A SOMATIC CELL HYBRID BETWEEN TWO BURKITT'S LYMPHOMA CELL LINES OF DIFFERENT INTERFERON SENSITIVITIES.

Lidin B, Lamon EW
(c/o Lamon) Dept. Microbiology, Cancer Res. and Training Center, Birmingham Veterans Admin. Hosp., Univ. Alabama in Birmingham, Birmingham, AL, 35294
Infect Immun; 36(2):847-849 1982

A somatic cell hybrid between two human Burkitt's lymphoma cell lines, Raji and Daudi, was infected with either Epstein-Barr virus or vesicular stomatitis virus after interferon treatment. Raji cells are resistant to the antiviral effects of exogenously added interferon, whereas Daudi cells are interferon sensitive. The Raji-Daudi hybrid showed an interferon sensitivity that was intermediary to that of the parental cells against both viruses. (Author abstract) (14 Refs)

91. ROLE OF DNA INCORPORATION IN THE MECHANISM OF ACTION OF 6-THIOGUANINE (6-TG) (MEETING ABSTRACT)

Drake S, Carpenter P, Nelson JA
Department of Experimental Pediatrics, M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):1566 1982

An antitumor agent, (6-TG) may alter cell viability and/or function due to incorporation into DNA. For example, the transforming activity of Bacillus subtilis DNA is reduced in a dose-dependent manner proportional to the incorporation of 6-TG. To test if other biological functions of DNA are altered by the base analog, a DNA virus (vaccinia) was grown in HeLa cells treated with 6-TG. The virus was extracted from the cells by sonication and purified by centrifugation on 25-60% sucrose density gradients. The buoyant density of the virus grown in the presence of 6-TG was more heterogeneous than control virus. However, no apparent physical abnormalities were discernible by electron microscopy, and the virions were not sensitive to deoxyribonuclease. Total infectious virus production was reduced 100-fold by treatment with 6-TG (30 ug/ml for 24 hrs) during infection; however, there was only a 6-fold reduction in particle formation. The ability of such particles to induce DNA synthesis in newly infected cells was also reduced markedly. These effects of 6-TG on vaccinia virus infectivity and viral genome expression may be a consequence of incorporation of the drug into the viral DNA. (no Refs)

GENERAL REVIEWS

92. HERPES SIMPLEX VIRUS: A CAUSE FOR CONCERN.

Alexander H
Dept. Lab. Medicine, Wesley Medical Center, Wichita, KS, 67214
Am J Med Technol; 48(4):241-245 1982

Laboratory facilities for the identification of herpes simplex virus (HSV) in tissue cultures should be available in every community. Evidence suggesting an association of genital HSV type 2 (HSV-2) infection with cervical carcinoma is primarily epidemiologic at present. Preliminary reports suggest that although topical treatment with acyclovir has little effect against recurrent HSV infections, systemic treatment of the initial infection significantly reduces the severity of the disease. However, this treatment does not eradicate latent HSV infections. (36 Refs)

93. PERSISTENCE OF EPSTEIN-BARR VIRUS INFECTION.

Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Symp Soc Gen Microbiol; 33:169-183 1982

General biology of Epstein-Barr virus (EBV) infection and persistence of EBV are discussed. Of the various types of infection which EBV can bring about, productive infection presents the least difficulty since it can be studied in vitro in the small number of cells of 'producer' lines which express virus replicative functions and because it has close similarities to the 'lytic' infections of most ordinary herpesviruses. The most difficult of the phenomena of persistence with EBV is that of the virus genome-containing B cell in the peripheral circulation of the normal seropositive individual. (72 Refs)

94. THE EPSTEIN-BARR VIRUS: HISTORICAL, BIOLOGIC, PATHOLOGIC AND ONCOLOGIC CONSIDERATIONS.

Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
Perspect Pediatr Pathol; 6:1-33 1981

The biological nature of Epstein-Barr virus (EBV) and clinical manifestations of human EBV infection and of several related disorders (infectious mononucleosis, fatal infectious mononucleosis, X-linked lymphoproliferative syndrome, Burkitt's lymphoma, nasopharyngeal carcinoma, ataxia-telangiectasia, cytomegalovirus) are reviewed. Immunoblastic sarcoma of B lymphocytes is discussed, and mechanisms to account for the failure of human immune defenses against EBV and subsequent development of carcinoma are proposed. (168 Refs)

95. SIGNIFICANCE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF LEUKEMIA, MYELOMA AND MALIGNANT LYMPHOMA.

Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
Lakartidningen; 79(15):1490-1492 1982

Studies on environmental factors in the etiology of leukemias, myelomas and lymphomas are reviewed. Ionizing radiation plays a role in the development of acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, myeloma, Hodgkin's disease and non-Hodgkin's lymphomas, but probably none in chronic lymphocytic leukemia. Viral etiology of chronic lymphocytic leukemia in farm workers and of Burkitt's lymphoma and of other non-Hodgkin's lymphomas is suspected. Hodgkin's disease was found to be overrepresented among men exposed to chemicals. (35 Refs) (In SWE)

96. PATHOBIOLOGY OF HEPATITIS B VIRUS.

Gerber MA, Thung SN
Dept. Pathology, Mount Sinai Hosp. and Sch. Medicine, City Univ. New York, New York, NY, 10029
Pathobiol Annu; 11:197-228 1981

Knowledge of the pathology of hepatitis B virus (HBV) and more recent findings are discussed. The amount of virus specified unique gene products may be limited, although combined mol wt of all polypeptides from hepatitis B surface antigens (HBsAg), hepatitis B core antigen, and a cryptic form of hepatitis B antigen (HBeAg) appear to exceed the coding capacity of the small HBV genome, which is approx 100,000 daltons of protein. Recent studies indicate that HBsAg and albumin receptor activity emerge simultaneously in hepatocellular cytoplasm of HBV infected patients and also in the cytoplasm, on the cell surface, and in the supernatant culture media of an HBsAg producing hepatocellular carcinoma (HCC) cell line. The 28 nanometer core particles of HBV can be isolated from circulating Dane particles (DP) by detergent treatment or from hepatocellular nuclei of infected liver. Observation of two populations of DP may be of great biological importance since only full particles with complete genome may be infectious, whereas empty particles may be defective and interfere with replication of homologous virus. HBeAg probably is an integral structural component of the HBV nucleocapsid, coded by the genome of the virus. In serum of HBV infected patients, HBeAg occurs free or in association with IgG, most likely as immune complexes. Diseases associated with HBV infection are acute and chronic hepatitis, and a variety of clinical syndromes may be associated with HBV infection. HBV may be one of the agents involved in the etiology of human HCC. HCC in man is highly correlated with prevalence of HBsAg carriers. Serologic markers of HBV infection are found in significantly higher frequency in patients with HCC, and tumor markers are detected in HCC cells. The possibility cannot be excluded that the virus plays a merely passive role in hepatocarcinogenesis. (228 Refs)

OTHER RELATED STUDIES

97. CYTOGENETICS OF MALIGNANT LYMPHOMAS.

Fonatsch C
Abteilung Humangenetik, Zentrum fur Kinderheilkunde und Humangenetik, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany
Dtsch Med Wochenschr; 107(12):468-471 1982

Methods and findings of cytogenetic analysis of malignant lymphomas (ML) are reviewed. Analysis consists of counting and structural examination of chromosomes using fluorescence or Giemsa banding techniques. Specific abnormalities characteristic of ML include loss or gain of certain chromosomes, presence of specific chromosomal alterations, and increased frequency of rearrangements of specific chromosomal regions. The most common extra chromosomes found in lymphomas are chromosomes 7, 3, and 12. The most common structural change is the marker 14q+, found in 64% of all lymphomas. Epstein-Barr virus (EBV) apparently is linked to chromosome 14, although the 14q+ marker is also found in EBV-negative lymphomas. Chromosome 14 is apparently involved in control of cell proliferation. Other chromosomes frequently showing alterations in lymphomas are 1, 6, and 11. Chromosome 1 is of particular importance in myeloid lymphomas. Chromosomal rearrangement alters gene function by a position effect. ML cells show a rate of sister chromatid exchange double of that found in normal cells, indicating chromosomal instability. Cytogenetic analysis can be used to differentiate ML from other lymphatic disorders. Staging of ML is aided by detection of chromosomal abnormalities in otherwise apparently normal biopsy tissue. Presence or absence of particular anomalies is of prognostic value, especially in cases of B-cell acute lymphatic leukemia and hairy-cell leukemia. (18 Refs) (In GER)

98. TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL 13-ACETATE: EFFECT ON COMPLEMENT AND EPSTEIN-BARR VIRUS RECEPTORS IN HUMAN LYMPHOBLASTOID CELL LINES.

Yamamoto N, Mitsuma T, Vogt A
(c/o Vogt) Institut fur Immunologie, Zentrum fur Hygiene, Universitat Freiburg, Hermann-Herder-Str. 11, 7800 Freiburg, W. Germany
JNCI; 68(3):385-390 1982

The effect of the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) on the C3 and Epstein-Barr virus (EBV) receptors in various human lymphoblastoid cells was investigated with the use of the erythrocyte-antibody-complement (EAC) rosette formation method and a quantitative bioassay for EBV receptors. TPA caused a significant decrease of C3 receptors in the cultures of both Raji and SB4 cells (by approximately 50% of the C3 receptors in untreated cultures at 10 ng/ml). Kinetic studies revealed that the rate of reduction was rather moderate but progressive, reaching a maximum 5 days after treatment with TPA. Kinetic studies showed that EBV receptors also decreased, similar to the reduction seen with C3 receptors after TPA treatment. The effect of TPA on the reduction of C3 receptors was observed not only in these cells but also in other EBV-positive B-cells, subclones of SB4 cells, and MOLT-4 cells. However, in an EBV-negative B-cell line, BJAB, EAC rosette formation was significantly enhanced. (Author abstract) (38 Refs)

99. THE FUNCTIONS OF ATYPICAL LYMPHOCYTES.

Hutt-Fletcher LM
Dept. Bacteriology and Immunology, Univ. North Carolina, Chapel Hill, NC, 27514
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

Descriptive work on atypical lymphocytes (AL) is reviewed and morphology, metabolism, surface markers, and occurrence of AL are presented. AL in infectious mononucleosis (IM) and the role of the Epstein-Barr virus in IM are discussed, along with other causes of IM. In view the presence of AL in moderate numbers in certain neoplastic conditions, an understanding of their generation and capabilities may provide new approaches for immunotherapy in malignant disease. (79 Refs)

100. CORRELATION OF INCREASED NUCLEASE ACTIVITY WITH ENHANCED VIRUS REACTIVATION.

Nishiyama Y, Maeno K, Yoshida S
Dept. Microbiology, Germfree Life Res. Inst., Nagoya Univ. Sch. Medicine, Nagoya, 464, Japan
Exp Cell Res; 138(2):485-489 1982

An increase in nuclease activity, which degraded both unirradiated and ultraviolet (UV)-irradiated DNA, was observed in the extract of monkey Vero cells after irradiation with an appropriate amount of UV. In contrast, no increase was observed with mouse L cells. Neither DNA polymerases nor uracil-DNA glycosylase was enhanced but rather suppressed by UV irradiation in both cell lines. Cytological studies showed that, in Vero cells, the reactivation of UV-irradiated herpes simplex virus was markedly enhanced by irradiating cells with UV before infection. However, no enhancement was observed with L cells. These results suggest that an increase in nuclease activity may be one of underlying mechanisms for the enhanced reactivation of DNA viruses. (Author abstract) (20 Refs)

101. VIROLOGIC STUDIES IN A CELL LINE DERIVED FROM HUMAN CERVICO-UTERINE CANCER.

Suarez G M, Ojeda F JM, Pincheira V J, Berrios S MS
Seccion Virologia, Departamento de Microbiologia y Parasitologia, Facultad de Medicina Norte, Universidad de Chile, Santiago, Chile
Rev Latinoam Microbiol; 23(2):91-95 1981

A new cell line was established in 1975 from a 35-yr-old patient with invasive carcinoma of the uterine neck (AdGo). The AdGo viral sensitivity was studied using DNA viruses like adeno Type 1 and Type 2, herpes simplex (HS) Type 1, HS Type 2; and RNA viruses like Echo 11, Coxsackie B, polio Type 1, Respiratory Syncytial virus and measles. Polio 1 and Echo 11 showed rapid cytopathic effect with 50% lysis within 48 hrs. Adenovirus Type 2 produced cytopathic effect in 72 hrs. Measles virus induced changes that could be detected on the nuclear level. The HS 1 and 2 produced cytopathic effect. Coxsackie B and Syncytial did not show effect even after 3 wk. Immunohemadsorption assay showed immunoglobulin receptors on surface of the AdGo. This effect was not observed with HeLa and HEp2 cell lines. Possible biologic significance of this observation was discussed. The AdGo is a new cell line that can be a new host for viral propagation and it is a stable in vitro system for the study of the relationship between the HS virus 2 and human carcinoma of the uterine neck. (24 Refs) (In SPA)

102. SERUM CONCENTRATIONS OF COMPLEMENT COMPONENTS 3 AND 4 IN LIVER DISEASE.

Lodi TZ, Hassan TJ, Zuberi SJ
PMRC Res. Centre, Jinnah Postgraduate Medical Cernter, Karachi, Pakistan
J Pakistan Med Assoc; 31(2):33-35 1981

Serum levels of complement components 3 (C3) and 4 (C4) were assayed in 20 healthy subjects, 20 patients with acute viral hepatitis (AVH: excluding fulminant hepatitis), 20 patients with cirrhosis (HC: 11/20 showed ascites), and 18 patients with primary liver cancer (PLC). In the AVH group, subnormal C3 levels (18/20 patients) were associated with massive hepatic necrosis. In patients with less severe AVH, the C3 values were less depressed and returned to normal upon recovery. HC was associated with an insignificant reduction of C3 levels (40% of patients) and a significant reduction of C4 (15%). Reduced C3 and C4 levels in the HC group were almost always associated with ascites. PLC was associated with an insignificant elevation of serum C3 (33.3% of patients) and a significant elevation of C4 (50%). It is suggested that the elevated C4 value in the PLC group may be associated with increased C4 synthesis by rapidly multiplying tumor cells, and that serum C4 levels may vary according to tumor size. In the acute and chronic liver diseases studied, serum C4 was a more sensitive indicator of complement abnormalities than C3. (15 Refs)

103. BREAST CANCER SKIN TEST ANTIGENS OF INCREASED SENSITIVITY PREPARED FROM VESICULAR STOMATITIS VIRUS-INFECTED TUMOR CELLS.

Austin FC, Boone CW, Levin DL, Cavins JA, Djerassi I, Rosner D, Case R, Klein E
NCI, NIH, Westwood Building, Room 10A07, Bethesda, MD, 20205
Cancer; 49(10):2034-2042 1982

Crude membrane (CM) extracts were prepared from five cultured breast tumor lines (MDA-MB-157, MDA-MB-231, ZR75-1, HSO578T, and MCF-7) which had been infected with vesicular stomatitis virus (VSV) to augment their antigenicity. In skin test trials, CM extracts of uninfected MCF-7 cells elicited positive responses in 0 of 13 (0%) tests in breast cancer patients, while VSV-MCF-7 elicited positive responses in 11 of the same 13 patients (84.6%). CM extracts of VSV-ZR75-1 and VSV-MCF-7 elicited greater delayed hypersensitivity responses (mm induration at 48 hr) in breast cancer patients than in patients with lung carcinoma or melanoma. Although the sensitivity of VSV-ZR75-1 was too low (10 of 28, or 35.7%, of tests positive) to be useful as a skin test antigen, VSV-MCF-7 elicited positive responses in 30 of 38 (78.9%) tests in breast cancer patients, as compared to 2 of 15 (13.3%) and 2 of 13 (15.4%) of tests in patients with lung carcinoma and melanoma, respectively. The 'virus-augmented' CM extract of cultured MCF-7 cells exhibited markedly greater sensitivity as compared to control MCF-7 extracts (p less than .005), with a high degree of specificity for breast cancer patients as compared to patients with the other neoplasms (p less than .00001). The results of skin testing with VSV-MCF-7 CM extracts demonstrated antigenic cross-reactivity with a large number of breast cancer patients, a finding of great importance for any potential immunotherapy and/or immunodiagnosis. (Author abstract) (27 Refs)

104. ARENAVIRUS (M.P.) THERAPY FOR MALIGNANT MELANOMA (MEETING ABSTRACT)

Brenner HJ, Rath P, Chaitchik S, Azizi E
Department of Oncology, Sheba Medical Center, Tel Hashomer, Israel
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

A lymphochorio meningitis arenavirus was grown on melanoma or Hela cells and termed MP. Nine patients with high risk (2 patients) or advanced stages (7 patients) were skin tested for hypersensitivity to recall antigens and to the media. All cases were then treated conventionally by surgery and for chemotherapy (DTIC (dacarbazine), Oncovin, BCNU (carmustine), Procarbazin) for persistent active disease. Live virus units (10(2)-10(3)) were injected IM or intralesional. Killed virus was then administered every 3-4 weeks for 1 year. All patients had an influenza like illness for 10 days. At 6 years, 4 patients are alive and well. Two patients had prolonged remission (14 months, 22 months). Three patients did not respond. These results are excellent and show promise of activity of the MP virus in the adjuvant setting. (no Refs)

105. MOLECULAR BIOLOGY OF ENVIRONMENTAL AROMATIC HYDROCARBONS. PROGRESS REPORT, JANUARY 1-JUNE 31, 1981.

Weiss SB
Chicago Univ., Chicago, IL
Molecular Biology of Environmental Aromatic Hydrocarbons. Progress Report, January 1 - June 31, 1981. Available from National Technical Information Service, Springfield, VA, as DE81029033:, 12 pp., 1981.

We have been examining the molecular biology of activated polycyclic aromatic hydrocarbons (PAH) in several different ways, using different biochemical systems. The projects involving these systems are as follows: (I) The binding of benzo(a)pyrene-7,8-dihydrodiol to phage DNA; (II) the binding of PAH-expoxide derivatives to single- and double-stranded 0X174 DNA and its effect on viral DNA infectivity; (III) the fate of benzo(a)pyrene adducts on SV40 DNA in infected monkey kidney cells; (IV) the effects of anti-BPDE on tRNA aminoacyl charging and protein synthesis. (Author abstract)

106. TREATMENT OF MALIGNANT GLIOMA WITH MUMPS VIRUS.

Yumitori K, Handa H, Yamashita J, Suda K, Otsuka S, Shimizu Y
Dept. Neurosurgery, Faculty Medicine, Univ. Kyoto, Kyoto, Japan
No Shinkei Geka; 10(2):143-147 1982

Six patients with malignant brain tumor were treated with mumps virus. Mumps virus was considered to be effective in three cases which were described in detail. First case: A 51-yr-old male with glioblastoma in the left thalamus was treated unsuccessfully with irradiation and chemotherapy after partial removal of the tumor. Mumps virus was administered, and 3 wk later showed 62% decrease of the tumor. Fifteen mo have passed since the treatment was started and the patient is still alive. Second case: A 46-yr-old male with a tumor in the corpus callosum was irradiated without operation. There was a 95% increase of the tumor. Mumps virus was administered, the tumor disappeared almost completely. The patient died 1 yr after the treatment was started, and death is ascribed to the metastatic lesion in the posterior fossa. Third case: An 18-yr-old female had a mass lesion in the left frontal lobe adjacent to the anterior horn of the lateral ventricle. Partial removal was performed and histological diagnosis was a mixed glioma consisting of ependymoma and oligodendroglioma. She was treated with mumps virus alone postoperatively. Follow-up CT scans showed an almost complete disappearance of the tumor. In the third case, administration of mumps virus alone induced an almost complete disappearance of the tumor on CT scans and improvement of clinical state. No effect of mumps virus was observed in other cases. The mechanism how mumps virus acts on tumor-bearing patients is not established b. immunological effect appears to be most likely. Several immunological parameters such as NK cell, killer T-cell, suppressor T-cell function and specific reaction to TSA will be examined. (9 Refs) (In JPN)

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SERIES CB04 No. 82/10

OCTOBER, 1982

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. ANALYSIS OF EPSTEIN-BARR VIRUS (EBV) OF P3HR-1: ISOLATION OF EBV WITH EBNA INDUCTION ABILITY IN HUMAN CORD LYMPHOCYTES AND WITHOUT EA INDUCTION ABILITY IN RAJI CELLS.

Yano S, Tanaka A, Takada K, Fujiwara S, Osato T, Nonoyama M
(c/o Nonoyama) Dept. Virology, Showa Univ. Res. Inst. Biomedicine Florida, 5180 113th Ave. N., Clearwater, FL, 33520
Virology; 119(2):392-398 1982

A subline of P3HR-1 cells was isolated through a prolonged (over 1 yr) propagation of the cells at a non-EBV-productive condition followed by cell cloning procedures. Cloned cells thus obtained, designated DHR1, produced EBV when brought back to the EBV-productive condition. Restriction enzyme analysis of the viral DNA revealed that DHR1 EBV is composed of an apparently homogeneous EBV population, and it displays a similar but not identical genome organization compared with HR-1 EBV. The characteristic biological properties of DHR1 EBV included the ability to induce EBV-associated nuclear antigen (EBNA) in human cord lymphocytes and the

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inability to induce EBV-associated early antigen (EA) in Raji cells. These are in striking contrast to the behavior of the parental HR-1 EBV. Thus, P3HR-1 cultures after a period of nonproductivity reinitiated the production of virus with an apparently homogeneous and unique population of EBV distinguishable from the original HR-1 virus. (Author abstract) (18 Refs)

2. PURIFICATION OF A NATIVE MEMBRANE-ASSOCIATED ADENOVIRUS TUMOR ANTIGEN.

Persson H, Katze MG, Philipson L
(c/o Katze) Molecular Biology and Genetics Unit, Graduate Sch. Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 42(3):905-917 1982

A 15,000-dalton protein was purified from HeLa cells infected with adenovirus Type 2. Proteins solubilized from a membrane fraction of lytically infected cells was used as the starting material for purification. Subsequent purification steps involved lentil-lectin, phosphocellulose, hydroxyapatite, DEAE-cellulose, and aminohexyl-Sepharose chromatographies. A monospecific antiserum, raised against the purified protein, immunoprecipitated a 15,000-dalton protein encoded in early-region E1B (E1B/15K protein) of the adenovirus Type 2 DNA. Tryptic finger print analysis revealed that the purified protein was identical to the E1B/15K protein encoded in the transforming part of the viral genome. The antiserum immunoprecipitated the E1B/15K protein from a variety of viral transformed cell lines isolated from humans, rats, or hamsters. The E1B/15K protein was associated with the membrane fraction of both lytically and virus-transformed cell lines and could only be released by detergent treatment. Furthermore, an 11,000-to 12,000-dalton protein that could be precipitated with the anti-E1B/15K serum was recovered from membranes treated with trypsin or proteinase K, suggesting that a major part of the E1B/15K protein is protected in membrane vesicles. Translation of early viral mRNA in a cell-free system, supplemented with rough microsomes, showed that this protein was associated with the membrane fraction also in vitro. (Author abstract) (47 Refs)

3. COVALENT AFFINITY LABELING BY PERODATE-OXIDIZED [ALPHA-32P]ATP OF THE LARGE-T PROTEINS OF POLYOMA AND SV40 VIRUSES.

Clertant P, Cuzin F
Centre de Biochimie du Centre National de la Recherche Scientifique, Universite de Nice, Parc Valrose, 06034 Nice, France
J Biol Chem; 257(11):6300-6305 1982

Incubation of crude extracts from cells lytically infected with polyoma virus in the presence of periodate-oxidized [alpha-32P]ATP led to the radioactive labeling of one main polypeptide immunoprecipitated by anti-T antigen antibodies. It was absent from extracts of mock-infected cells and exhibited an apparent Mr value of 105,000 identical with that of the large-T viral protein. This polypeptide was unambiguously identified as large-T on the basis of the heat sensitivity of the in vitro labeling in extracts from cells infected with a tsa mutant. The amount of incorporated radioactivity was found to increase linearly with that of infected cell extract and with the incubation time. Labeling resulted from the specific binding of an oxidized ATP molecule to a nucleotide binding site of the large-T protein, since it was efficiently competed by unlabeled ATP. Study of the dependence on the concentration of oxidized ATP evidenced a first order kinetic for the labeling reaction. Similar results were obtained for the large-T protein of SV40 virus. (Author abstract) (32 Refs)

4. FINE STRUCTURE OF VIRUS CHROMATIN IN THIN SECTIONS OF SV40-INFECTED CELLS: A CYTOCHEMICAL AND AUTORADIOGRAPHICAL STUDY.

Puvion-Dutilleul F, Puvion E
Institut de Rechereches Scientifiques sur le Cancer, CNRS, F-94802 Villejuif Cedex, France
J Gen Virol; 59(part2):235-244 1982

The ultrastructural organization of virus chromatin was studied within nuclei prepared from CV1 cells (cultured monkey kidney cells) lytically infected with SV40 virus (simian virus 40) by a procedure which allows a mild loosening of nucleoproteins. In addition to dispersed host components, DNA-containing nucleoplasmic structures could be identified as virus chromatin both standard staining for structure and specific staining for DNA clearly revealed in thin sections the nucleosomal structure of well-extended virus chromatin as well as alignments of virions on host chromatin. In addition, replicating and transcribing virus chromatins were abundant as revealed by high-resolution autoradiography. Therefore, the procedure of loosening of nucleoproteins used in this report also preserves the active SV40 chromatin and allows the in situ visualization in Epon sections of transcription and replication of the virus genome. (Author abstract) (25 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

5. DNA FROM CELLS INFECTED WITH RETROVIRUS D AND FROM HUMAN TUMORS - INDUCER OF THE SYNTHESIS OF NEW NONVIRION ANTIGEN.

Kosiakova NP, Pavliuchenkova RP
D. I.Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (2):230-234 1982

Role of DNA of retrovirus D in the synthesis of new nonvirion antigen was studied in HEp-2 cells chronically infected with retrovirus D and in cultured cells of various human tumors. Transfection technique showed that the synthesis of new surface retrovirus D-associated antigen was induced by DNA. DNA isolated from normal human tissues failed to induce synthesis of the antigen. (22 Refs) (In RUS)

6. CHARACTERISTICS OF HODGKIN'S DISEASE-DERIVED CELL LINES.

Diehl V, Kirchner HH, Burrichter H, Stein H, Fonatsch C, Gerdes J, Schaadt M, Heit W, Uchanska-Ziegler B, Ziegler A, Heintz F, Sueno K
Hamatologie/Onkologie, Medizinische Hochschule, Karl-Wiechert-Allee 6, 3000 Hannover, W. Germany
Cancer Treat Rep; 66(4):615-632 1982

In the last 3 yr we were able to establish five long-term in vitro cell cultures from biopsy specimens taken preterminally from four patients with histologically proven Hodgkin's disease (nodular sclerosing type, clinical Stage IVB). Four of the lines are continuously proliferating in vitro; one culture stopped growth for unknown reasons after 7 months. When culture conditions were modulated, the first culture, L 428, gave rise to two sublines: L 428 KS, after adaptation to calf serum, and L 428 KSA, permanently growing as an adherent monolayer line after treatment with a phorbol ester (12-O-tetradecanoylphorbol-13-acetate) for 3 wk. Cell-marker analysis by conventional means (SIg, cIg, rosette formation, Epstein-Barr virus reactivity, cytochemistry, phagocytosis, and lysozyme production) and with monoclonal antibodies directed against various human lymphoid, myeloid, and monocytoid antigens showed that the tested cell lines are clearly different from all hitherto described hematopoietic lines; they most likely represent a cell type resembling an early myeloid-monocytoid progenitor cell. Conditioned medium of the L 428 cells and its two sublines showed colony-stimulating factor activity and suppression of spontaneous cell-mediated cytolysis of L 428 KS and K 562 cells. (Author abstract) (26 Refs)

7. EPSTEIN-BARR VIRUS-SPECIFIED POLYPEPTIDES IN BURKITT LYMPHOMA/SOMATIC CELL HYBRIDS (MEETING ABSTRACT)

Durnford JM, Scanlon PA, Glaser R
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

Adding 5'-iododeoxyuridine (IUDR) to cultured Burkitt lymphoma/somatic cell hybrids (D98/HR-1) leads to expression of Epstein-Barr virus (EBV) early antigen (EA). When the drug is removed, the cells synthesize virus DNA, virus capsid antigen (VCA), and ultimately virus particles. The EBV-specified polypeptides present in cells before and after removal of IUDR were immunoprecipitated with serum having high antibody titers against the EBV nuclear antigen (EBNA), EA, and VCA. These polypeptides were then analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Their cellular location was determined by isolating nuclear and cytoplasmic fractions from the induced cells prior to radioimmunoprecipitation. The predominant polypeptides associated with the synthesis of EA had apparent molecular weights of 125 and 82 kilodaltons, respectively. The larger polypeptide was found primarily in the nucleus, whereas the smaller polypeptide was found in both nuclear and cytoplasmic fractions. Two prominent polypeptides having apparent molecular weights of 141 and 133 kilodaltons were detected after the initiation of virus DNA synthesis. These appear to be the major components of VCA and may correspond to VP6 and VP7. In addition to these four prominent polypeptides, several additional polypeptides were specifically immunoprecipitated. (1 Ref)

8. SUPPRESSION OF FIBRONECTIN SYNTHESIS BY AN EARLY FUNCTION(S) OF HUMAN CYTOMEGALOVIRUS.

Ihara S, Saito S, Watanabe Y
Dept. Molecular Biology, Tokai Univ., Sch. Medicine, Bohseidai, Isehara, 259-11, Japan
J Gen Virol; 59(part2):409-413 1982

Labeling of fibronectin with [3H]leucine and its isolation by immunoprecipitation followed by electrophoresis on gels showed that fibronectin synthesis was specifically suppressed in human embryonic cells infected with human cytomegalovirus. Degradation or release of pre-existing fibronectin into the medium was not affected. The inhibition of fibronectin synthesis was also observed when cells were infected with a DNA-minus temperature-sensitive mutant at the non-permissive temperature but not observed in infection with uv-irradiated virus, suggesting the involvement of the expression of an early virus function(s). This capacity of the virus may be implicated in the virus-induced early cell rounding. (Author abstract) (16 Refs)

9. A PRIMATE MODEL FOR THE STUDY OF RETINOBLASTOMAS (MEETING ABSTRACT)

Kalter SS, Mukai N, Heberling RL
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

Although several primate viruses have been demonstrated to be oncogenic in one or another experimental host, causation of human tumors is still equivocal. Primate adenoviruses, long known to be oncogenic in various rodent systems, have been previously shown to produce retinoblastoma-like neoplasms in rats. Other investigators have demonstrated that adenovirus type 12 was capable of transforming hamster neural retina cell in vitro. It was of interest, therefore, to ascertain if human retinoblastomas suspected of being of viral origin, could be induced in an experimental animal. We chose the baboon (Papio cynocephalus) principally because of the intensive amount of information available on the virology of this species, as well as, their availability as newborns. Further, in contrast to rodents, newborn baboons (like the human) have mature retinas. Approximately one year after inoculation (all baboons were inoculated intraocularly within 24 hours after birth) with 0.05 to 0.1 ml of 10(8) TCID50 Ad12 virus, baboons started exhibiting light reflection in the inoculated eyes. Enucleation of inoculated eyes approx 36-46 months after inoculation clearly demonstrated the production of retinal tumors with complete rosettes characteristic of photoreceptor differentiation. (no Refs)

10. CHARACTERISTICS OF SKIN AND TUMOR FIBROBLASTS FROM NEUROFIBROMATOSIS PATIENTS.

Riccardi VM, Margos VA
Robert J. Kleberg, Jr. Center Human Genetics, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
Adv Neurol; 29:191-198 1981

Cell culture studies using cells from skin, cutaneous neurofibromas, and other tumors of neurofibromatosis patients are reviewed. Explant growth of skin and tumor specimens, cytogenetic analyses, transmission electron microscopy, Simian virus-40 transformation, skin fibroblast proliferation, amino acid uptake studies, and amino acid analogue treatment experiments are discussed. (11 Refs)

11. IS TRANSFORMATION ASSOCIATED WITH AN INCREASED ERROR FREQUENCY IN MAMMALIAN CELLS?

Pollard JW, Harley CB, Chamberlain JW, Goldstein S, Stanners CP
Dept. Biochemistry, Queen Elizabeth Coll., Univ. London, Campden Hill, London W8 7AH, England
J Biol Chem; 257(11):5977-5979 1982

Acute starvation of mammalian cells for amino acids results in translational errors that may be detected by two-dimensional polyacrylamide gel electrophoresis. Using this as an assay for error frequency in mammalian cells, we investigated the hypothesis that neoplastic transformation was associated with an increased error frequency which in turn leads to an increased mutation rate and a decreased efficiency of regulatory controls (phenomena of tumor progression). Although we found that transformation was not always associated with an increased level of mistranslation we showed that SV40 transformation increased the level of translational errors in all cell types tested. (Author abstract) (27 Refs)

12. REACTIVATION OF CHRONIC HEPATITIS B VIRUS INFECTION BY CANCER CHEMOTHERAPY (MEETING ABSTRACT)

Hoofnagle JG, Dusheiko GM, Schafer DF, Micetich KC, Young RC, Costa J

National Institutes of Health, Bethesda, MD

32nd Annual Meeting of the American Association for the Study of Liver Diseases, November 5-8, 1981, Chicago, Illinois. American Association for the Study of Liver Diseases 97 pp., 1981.

Two patients referred for cancer chemotherapy were found to be chronic asymptomatic hepatitis B surface antigen (HBsAg) carriers at initial presentation. They had normal serum bilirubin, albumin and aminotransferase levels. Their sera were positive for HBsAg but were negative for hepatitis B e antigen (HBeAg) and hepatitis B virus specific DNA and DNA polymerase activity. Both patients were positive for antibody to HBeAg (anti-HBe). Liver biopsy in one patient revealed normal hepatic architecture and many 'ground glass' hepatocytes. The first patient was treated with cyclophosphamide, actinomycin, bleomycin, vincristine and cis-platinum for testicular carcinoma. The second was given cyclophosphamide, vincristine, prednisone and procarbazine (C-MOPP) for nodular mixed lymphoma. Both patients developed acute, icteric hepatitis within three months of starting cycled chemotherapy. This appeared to be due to a reactivation of type B hepatitis, in that both cases were accompanied by a marked increase in HBsAg titer and the appearance of hepatitis B virus DNA and DNA polymerase in the serum. Neither patient had received blood transfusions and both remained negative for antibody to hepatitis A virus. The two patients recovered. One eventually became HBsAg negative and developed antibody to HBsAg (anti-HBs). The second patient developed a second bout of severe acute hepatitis accompanied by the reappearance of hepatitis B virus DNA and DNA polymerase as well as HBeAg after a second course of chemotherapy. (no Refs)

VIRUS REPLICATION AND EXPRESSION

13. SIMILARITY OF EPSTEIN-BARR VIRUS EARLY POLYPEPTIDES INDUCED BY VARIOUS TUMOR PROMOTERS.

Kawanishi M, Ito Y

(c/o Ito) Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan

Cancer Lett; 16(1):19-23 1982

The induction of Epstein-Barr virus (EBV) early antigen in EBV-harboring but nonproducing Raji cells by n-butyrate in combination with a variety of tumor promoters is reported. The overall pattern of polypeptides induced by Croton tiglium extract, Euphorbia lathyris extract, croton oil, teleocidin B, and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was strikingly similar. While the plant diterpenes (eg, TPA) differ completely in structure from teleocidin B, an indole-alkaloid, both types of compounds are tumor promoting agents and both activate EBV expression. EBV early polypeptides induced in the EBV-genome harboring Raji cells by these agents are identical. These results suggest that dissimilar tumor promoters act through a common pathway that is independent of structural considerations. (13 Refs)

14. EXPRESSION OF ADENOVIRAL GENETIC INFORMATION IN PRODUCTIVELY INFECTED CELLS.

Flint SJ

Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544

Biochim Biophys Acta; 651(2/3):175-208 1982

Recent advances in the understanding of mechanisms and regulation of adenoviral gene expression are reviewed. Topics discussed include the structure of adenoviral early genes (early regions E1-E4 and expression of additional genes during early phase of infection), synthesis of adenoviral early messenger RNA species, regulation of adenoviral early gene expression, organization and expression of adenoviral late genes, the early to late transition, structure and function of adenoviral 'promoter' sites, and the virus associated (VA)-RNA genes. (225 Refs)

15. PRESENCE IN GROWTH-ARRESTED CELLS OF CELLULAR PROTEINS THAT INTERACT WITH SIMIAN VIRUS 40 SMALL-T ANTIGEN.

Rundell K

Dept. Microbiology and Immunology, Northwestern Univ., Chicago, IL, 60611

J Virol; 42(3):1135-1137 1982

Two cellular proteins, 56K and 32K, found in association with simian virus 40 small-t antigen were not induced by viral infection. In addition, the proteins were expressed by cells in the growth arrest period, a time in which small-t function is of importance in infection and transformation. (Author abstract) (12 Refs)

16. RECURRENT GENITAL HERPES SIMPLEX VIRUS INFECTION IN PREGNANCY: INFANT OUTCOME AND FREQUENCY OF ASYMPTOMATIC RECURRENCES.

Vontver LA, Hickok DE, Brown Z, Reid L, Corey L

Dept. Obstetrics and Gynecology, RH-20, Univ. Washington, Seattle, Washington, 98195

Am J Obstet Gynecol; 143(1):75-84 1982

Eighty pregnant patients with a history of recurrent genital herpes simplex virus (HSV) infection were followed up with frequent genital examinations and cultures for HSV during their pregnancies. Recurrences of genital HSV during pregnancy were documented in 67 patients. Ninety-six percent of these had external genital lesions noted at some time during their pregnancy. One hundred eighty-six (93%) of the 199 recurrences of the disease were associated with external genital lesions. Of 13 episodes of asymptomatic viral shedding documented in this patient population, 6 were from the vulva alone, 5 were from the cervix alone, and 2 were from both the vulva and the cervix. Of 11 episodes of cervical HSV shedding, 7 were asymptomatic and 4 were associated with external symptomatic lesions. Despite frequent recurrences of genital HSV infection during pregnancy, all study patients were delivered at term, and although they had a high rate of delivery by cesarean section (32.5%), the outcome of their infants was good. (Author abstract) (14 Refs)

17. CLINICAL AND VIROLOGICAL FEATURES OF HERPES GENITALIS IN JAPANESE WOMEN.

Ishiguro T, Ozaki Y, Matsunami M, Funakoshi S
Dept. Obstetrics and Gynecology, Shiga Univ. of Medical Science, Seta, Ohtsu 520-21, Japan
Acta Obstet Gynecol Scand; 61(2):173-176 1982

We report herein clinical and virological findings in 35 Japanese women with a confirmed herpes genitalis. The frequency of herpes genitalis was 0.24% in our obstetrical and gynecological outpatient clinic, while that in cancer screening clinics was 0.01%. Eight percent of all patients were between 20 and 49 yr of age (median age of 38.5 yr). Genital herpes was detected more frequently in summer and autumn. Virus isolations were carried out in 20 patients and 13 were positive (65.0%). Of 13 genital isolates with positive cultures, 7 (53.8%) were identified as herpes simplex virus Types 1 (HSV-1) and 6 (46.2%) as herpes simplex virus Type 2 (HSV-2). Two virgins were diagnosed virologically and cytologically as having progenital herpes, and in these two women, HSV-1 was isolated by the virus isolations. Lack of antibodies to either virus was higher in HSV-1 type infection. These studies together with previous findings show that both clinical and virological features of genital herpes differ between Japanese and Caucasian or black women. These differences are attributed to some extent to sexual patterns of behavior in the different races. (Author abstract) (11 Refs)

18. ASPECTS OF THYMIDINE METABOLISM AND FUNCTION IN CULTURED MAMMALIAN CELLS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 1.

Baybutt HN, Murray BA, Pearson CK
Dept. Biochemistry, Univ. Aberdeen, Marischal Coll., Aberdeen, AB9 1AS, Scotland
J Gen Virol; 59(part2):223-234 1982

We have investigated aspects of thymidine metabolism and function in cultured mammalian cells infected with herpes simplex virus under conditions in which virus DNA synthesis was either permitted, or was prevented by inhibiting the virus-induced DNA polymerase with phosphonoacetate. In 30 min pulse-labeling experiments the rates of [3H]thymidine transport into cells and its subsequent phosphorylation both reached max values about 6 hr after infection. During the next 17 hr these rates remained relatively constant in the absence of phosphonoacetate but declined to about 50% of the 6 hr value in the presence of this inhibitor. When the radioactive thymidine was present continuously throughout the infection the accumulated intracellular acid-soluble radioactivity reached max values at about 9 hr. In the absence of phosphonoacetate this declined thereafter, but it remained relatively constant when virus DNA synthesis was prevented. This suggests some established equilibrium between the continuing entry of thymidine into cells and its subsequent removal by excretion. Excretion of thymidine-derived radioactivity was initially established by determining the fate of isotopically labeled host cell DNA. During 24 hr of infection about 50% of the host cell DNA was rendered acid-soluble and of this 60 to 70% was excreted from the cells. High pressure liquid chromatographic analysis of the intracellular acid-soluble radioactivity showed only phosphorylated thymidine derivatives, whereas the excreted radioactivity was exclusively in thymidine. Excretion of intracellular radioactive molecules derived directly from [3H]thymidine in the medium was also observed, but only when virus DNA synthesis was inhibited with phosphonoacetate. Simple kinetic studies with the purified virus-induced DNA polymerase showed that a straight line double-reciprocal plot was obtained when dGTP was used as the limiting substrate (Km = 0.8 uM), but that a biphasic plot was obtained when dTTP was limiting. (28 Refs)

19. HERPES SIMPLEX INFECTIONS: A COMBINED GP AND SPECIALIST VIEW.

Piterman L, Marks R
326 South Road, Moorabbin 3189, Australia
Aust Fam Physician; 11(3):197-202 1982

Pathology, immunity, incidence, and management of herpes simplex infections are discussed from the points of view of the general practitioner and the specialist. The nature and therapy for primary types 1 and 2 and recurrent infections are reviewed. No cure exists, but treatment with topical and systemic antiviral agents, antibacterial agents to control secondary infection, analgesia, and patient counseling contribute to effective management of the disease throughout its course. (6 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

20. NUCLEOTIDE SEQUENCE OF THE TRANSFORMING GENE OF SIMIAN SARCOMA VIRUS.

Devare SG, Reddy EP, Robbins KC, Andersen PR, Tronick SR, Aaronson SA
Lab. Cellular and Molecular Biology, Natl. Cancer Inst., Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(10,part1):3179-3182 1982

The sequence of the transforming region of simian sarcoma virus (SSV) has been determined by using molecularly cloned viral DNA. This region encompassed the 1.0-kilobase pair woolly monkey cell-derived insertion sequence, v-sis, and flanking simian sarcoma-associated viral (SSAV) sequences. A 675-nucleotide-long open reading frame commenced 19 nucleotides within the SSAV sequences to the left of the v-sis helper viral junction and terminated within v-sis itself. Possible promoter and acceptor splice signals were detected in helper viral sequences upstream from this open reading frame, and potential polyadenylylation sites were identified downstream both within v-sis and in helper viral sequences beyond v-sis. The recombinational event that led to the generation of SSV occurred in the middle of two functional codons, indicating that SSAV provided the regulatory elements for transcription as well as the initiation codon for translation of SSV cell-derived transforming sequences. (Author abstract) (28 Refs)

21. NUCLEOTIDE SEQUENCE ANALYSIS OF THE LONG TERMINAL REPEAT OF INTEGRATED SIMIAN SARCOMA VIRUS: EVOLUTIONARY RELATIONSHIP WITH OTHER MAMMALIAN RETROVIRAL LONG TERMINAL REPEATS.

Devare SG, Reddy EP, Law JD, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20205
J Virol; 42(3):1108-1113 1982

Nucleotide sequence analysis of the long terminal repeat (LTR) of the integrated simian sarcoma virus showed that the simian sarcoma virus LTR comprised 504 nucleotides with an inverted repeat of seven bases at its 5' and 3' termini. At the site of simian sarcoma virus integration, cellular flanking sequences adjacent to the proviral LTR contained a direct repeat of four bases. A 13-base sequence after the 5' LTR was found to be complementary to prolyl tRNA, suggesting that tRNA-Pro may serve as the primer for reverse transcription of simian sarcoma virus RNA. The U5 and R regions, derived respectively from the 5' end and terminally redundant sequences of the viral RNA, were found to have similar organization and sequence homology close to that of Moloney murine sarcoma virus or Moloney murine leukemia virus. These results indicate that regions within LTRs with known functionally important sequences have been most well conserved during retrovirus evolution. (Author abstract) (45 Refs)

22. ISOLATION OF HUMAN ONCOGENE SEQUENCES (V-FES HOMOLOG) FROM A COSMID LIBRARY.

Groffen J, Heisterkamp N, Grosveld F, Van de Ven W, Stephenson JR
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Science; 216(4550):1136-1138 1982

To define the human homolog (or homologs) of transforming sequences (v-fes gene) common to Gardner (GA) and Snyder Theilen (ST) isolates of feline sarcoma virus (FeSV), a representative library of human lung carcinoma DNA in a cosmid vector system was constructed. Three cosmid clones were isolated containing GA/ST FeSV v-fes homologous cellular sequences, within 32-to 42-kilobase cellular inserts representing 56 kilobases of contiguous human cellular DNA. Sequences both homologous to, and colinear with, GA or ST FeSV v-fes are distributed discontinuously over a region of up to 9.5 kilobases and contain a minimum of three regions of nonhomology representing probable introns. A thymidine kinase selection system was used to show that, upon transfection to RAT-2 cells, the human c-fes sequence lacked detectable transforming activity. (Author abstract) (24 Refs)

23. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW
Imperial Coll. Science and Technology, London SW7 2BZ, England
Nature; 297(5866):451-453 1982

Characterization of cellular oncogenes is reviewed. Oncogenes exhibit target specificity within a lineage. Recombinant DNA technics have been applied to the cloned human bladder carcinoma oncogene. The relationship between cellular oncogenes and proto-oncogenes (genes detected by transfection) has been studied. Retrovirus onc genes have been cloned and used to analyze DNA of NIH cells transformed by a variety of cellular oncogenes. The cloned human bladder carcinoma oncogene has been shown to be homologous to ras, the transforming gene of Harvey murine sarcoma virus. Mechanisms of oncogene activation and action are discussed. (19 Refs)

24. HUMAN EJ BLADDER CARCINOMA ONCOGENE IS HOMOLOGUE OF HARVEY SARCOMA VIRUS RAS GENE.

Parada LF, Tabin CJ, Shih C, Weinberg RA
Center for Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Nature; 297(5866):474-478 1982

Examination of homologies between retroviral oncogenes and transforming sequences defined by transfection reveals that the human bladder carcinoma (EJ) oncogene is homologous to the Harvey sarcoma virus oncogene (ras). Structural analysis limits the region of homology to a 3.0-kilobase SacI fragment of the EJ oncogene. Both EJ and ras DNA probes detect similar transcripts in transfectants derived from bladder carcinoma cell lines. (Author abstract) (42 Refs)

25. EXPRESSION OF HUMAN BETA-INTERFERON CDNA UNDER THE CONTROL OF A THYMIDINE KINASE PROMOTER FROM HERPES SIMPLEX VIRUS.

Reyes GR, Gavis ER, Buchan A, Raj NB, Hayward GS, Pitha PM
Dept. Pharmacology and Experimental Therapeutics, John Hopkins Univ. Sch. Medicine, 725 N. Wolfe St., Baltimore, MD, 21205
Nature; 297(5867):598-601 1982

Transcription of human beta-interferon (IFN-beta) gene and the induction of the gene after replacing the normal 5' flanking sequences with a defined promoter segment from another gene were examined. For this purpose the coding portion of the IFN-beta gene was inserted downstream from the promoter sequence and RNA start site of the thymidine kinase (TK) gene from herpes simplex virus type 1. Expression of interferon activity under the control of the viral TK promoter in this chimeric plasmid was demonstrated by microinjection into nuclei of Xenopus oocytes and by transfection into cells followed by superinfection with herpes simplex virus. (32 Refs)

26. MAPPING OF AN ADENOVIRUS FUNCTION INVOLVED IN THE INHIBITION OF DNA DEGRADATION.

Lai Fatt RB, Mak S
Dept. Biology, McMaster Univ., Hamilton, Ontario, L8S 4K1, Canada
J Virol; 42(3):969-977 1982

A function involved in the inhibition of DNA degradation has been assigned through complementation tests to a product of region E1b of the adenovirus genome (between 4.5 and 10.5 map units). DNA degradation induced by the adenovirus Type 12 (Ad12) cyt mutant H12cyt70 and the Ad5 early deletion mutant dl313 (with the deletion between 3.5 and 10.7 map units) was inhibited by coinfection with Ad5 region E1a (between 0 and 4.5 map units) mutants dl312 and hr1 and region E1b mutant hr6. The defect of inhibition of DNA degradation in Ad5 dl313 was also complemented in 293 cells. This DNase-inhibitory function does not appear to involve polypeptide IX or the 58,000-dalton polypeptide. Wild-type Ad12 induced DNA degradation in hamster embryo cells, suggesting that the DNase-inhibitory function is not expressed in these nonpermissive cells. Additional evidence suggests the involvement of a second viral product which positively influences the DNase activity and which appears to be an early function. (Author abstract) (47 Refs)

27. CHARACTERIZATION OF A TEMPERATURE-SENSITIVE FIBER MUTANT OF TYPE 5 ADENOVIRUS AND EFFECT OF THE MUTATION ON VIRION ASSEMBLY.

Chee-Sheung CC, Ginsberg HS
(c/o Ginsberg) Dept. Microbiology and Cancer Center, Columbia Univ., Coll. Physicians and Surgeons, New York, NY, 10032
J Virol; 42(3):932-950 1982

A temperature-sensitive, fiber-minus mutant of Type 5 adenovirus, H5ts142, was biochemically and genetically characterized. Genetic studies revealed that H5ts142 was a member of one of the three apparent fiber complementation groups which were detected owing to intracistronic complementation. Recombination analyses showed that it occupied a unique locus at the right end of the adenovirus genetic map. At the nonpermissive temperature, the mutant made stable polypeptides, but they were not glycosylated like wild-type fiber polypeptides. Sedimentation studies of extracts of H5ts142-infected cells cultured and labeled at 39.5 C indicated that a limited number of the fiber polypeptides made at the nonpermissive temperature could assemble into a form having a sedimentation value of 6S, but that this 6S structure was not immunologically reactive. When H5ts142-infected cells were shifted to the permissive temperature, 32 C, fiber polypeptides synthesized at 39.5 C were as capable of being assembled into virions as fibers synthesized in wild type-infected cellsy. In H5ts142-infected cells incubated at 39.5 C, viral proteins accumulated and aggregated into particles having physical characteristics of empty capsids. When the infected culture was shifted to 32 C, DNA appeared to enter the empty particles and complete virions developed. The intermediate particles obtained had the morphology of adenoviruses, but they contained less than unit-length viral genomes as measured by their buoyant density in a CsCl density gradient and the size of their DNA as determined in both neutral and alkaline sucrose gradients. The reduced size of the intermediate particle DNA was demonstrated to be the result of incompletely packaged DNA molecules being fragmented during the preparative procedures. Hybridization of labeled DNA extracted from the intermediate particles to filters containing restriction fragments of the adenovirus genome indicated that the molecular left end of the viral genome preferentially entered these particles. (64 Refs)

28. AN ADENOVIRUS AGNOGENE.

Virtanen A, Alestrom P, Persson H, Katze MG, Pettersson U
Dept. Microbiology, Biomedical Center, Univ. Uppsala, Box 581, S-751 23 Uppsala, Sweden
Nucleic Acids Res; 10(8):2539-2548 1982

The nucleotide sequence of a 550 base pairs long segment, located between map positions 21 and 22.5 in the adenovirus Type 2 genome has been determined. S1 nuclease mapping and sequence analysis of cDNA copies of adenovirus mRNA demonstrated that the established sequence includes the i-leader which is spliced to the 5'-end of certain adenovirus mRNAs. The i-leader which is 440 nucleotides long contains an open transitional reading frame which is preceded by an AUG triplet and which terminates in the third segment of the tripartite leader. A polypeptide with the same mol wt as predicted from the DNA sequence was identified by in vitro translation of mRNA which had been selected by hybridization to DNA fragments, containing sequences from the i-leader. The results thus suggest that the i-leader, unlike other adenovirus leader segments, is used for translation. (Author abstract) (27 Refs)

29. EXPRESSION OF EUKARYOTIC VIRAL AND CELLULAR GENES.

Pettersson RF, Kaariainen L, Soderlund H, Oker-Blom N
Dept. Virology, Univ. Helsinki, Helsinki, Finland
Expression of Eukaryotic Viral and Cellular Genes. London, Academic Press, 324 pp., 1981.

Recent advances in molecular virology, molecular genetics, and recombinant DNA research are combined in a discussion of expression of eukaryotic viral and cellular genes. Structure and expression of DNA virus genes are reviewed with respect to molecular analysis of adenovirus transformation, control of adenovirus messenger (m)RNA production by differential transcription and differential stability of mRNA, an early adenovirus glycoprotein and its association with transplantation antigens, the control of adenovirus early gene expression, and mutational analysis of regulatory elements of simian virus 40. Retrovirus genes are discussed with respect to OK 10 virus-transformed bone-marrow-derived cell line, the transforming insert in the Abelson murine leukemia virus genome, and DNA intermediates in the replication of retroviruses. RNA virus genes are discussed with respect to the genome of single-stranded messenger-sense RNA viruses, influenza virus, capped cellular RNAs, drift and shift of influenza A-type virus, vesicular stomatitis virus and host cell phosphoproteins, initiation of eukaryotic protein synthesis, alphavirus gene products, Semliki Forest virus, RNA containing heterogeneous 5'-terminal nucleotide sequences, and Semliki Forest virus defective interfering RNA using DNA copies. Eukaryotic genes are discussed with respect to structure, organization and developmental expression of chorion multigene families, gene amplification and methotrexate resistance, RNA-protein complexes precipitated by Lupus antibodies, promoter sequences, expression of cloned eukaryotic genes in microorganisms, human genomic DNA-encoding Pro-opiomelanocortin, and functional yeast minichromosomes containing centromeric DNA. (701 Refs)

30. ATTENUATION IN THE CONTROL OF SV40 GENE EXPRESSION.

Hay N, Skolnik-David H, Aloni Y
Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Cell; 29(1):183-193 1982

Nuclei and viral transcriptional complexes were prepared from cells infected with simian virus 40 and incubated in vitro in the presence of alpha-32P-UTP. The in vitro elongated viral RNA appeared with a peak of 5S in sucrose gradients and hybridized preferentially to a promoter-proximal region of SV40 DNA. Treatment of infected cells with proflavine led to transcription of elongated RNA, while treatment of cells with 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole, a drug known to enhance premature termination, augmented accumulation of the promoter-proximal RNA. The in vitro elongated RNA produced a major band of 93-95 nucleotides in length in acrylamide gel. This RNA was found to map between the major initiation site at nucleotide 243 and nucleotides 335-337. The significance of these observations with respect to the transcription termination signal and the control of SV40 gene expression is discussed. (Author abstract) (62 Refs)

31. RECOGNITION SITES OF EUKARYOTIC DNA TOPOISOMERASE I: DNA NUCLEOTIDE SEQUENCING ANALYSIS OF TOPO I CLEAVAGE SITES ON SV40 DNA.

Edwards KA, Halligan BD, Davis JL, Nivera NL, Liu LF
(c/o Liu) Dept. Physiological Chemistry, Johns Hopkins Medical Sch., Baltimore, MD, 21205
Nucleic Acids Res; 10(8):2565-2576 1982

Eukaryotic DNA topoisomerase I introduces transient single-stranded breaks on double-stranded DNA and spontaneously breaks down single-stranded DNA. The cleavage sites on both single and double-stranded SV40 DNA have been determined by DNA sequencing. Consistent with other reports, the eukaryotic enzymes, in contrast to prokaryotic Type I topoisomerases, links to the 3'-end of the cleaved DNA and generates a free 5'-hydroxyl end on the other half of the broken DNA strand. Both human and calf enzymes cleave SV40 DNA at identical and specific sites. From 827 nucleotides sequenced, 68 cleavage sites were mapped. The majority of the cleavage sites were present on both double and single-stranded DNA at exactly the same nucleotide positions, suggesting that the DNA sequence is essential for enzyme recognition. By analyzing all the cleavage sequences, certain nucleotides are found to be less favored at the cleavage sites. There is a high probability to exclude G from positions-4,-2,-1 and +1, T from position-3, and A from position-1. These five positions (-4 to +1 oriented in the 5' to 3' direction) around the cleavage sites must interact intimately with topo I and thus are essential for enzyme recognition. One topo I cleavage site which shows an atypical cleavage sequence maps in the middle of a palindromic sequence near the origin of SV40 DNA replication. It occurs only on single-stranded SV40 DNA, suggesting that the DNA hairpin can alter the cleavage specificity. The strongest cleavage site maps near the origin of SV40 DNA replication at nucleotide 31-32 and has a pentanucleotide sequence of 5'-TGACT-3'. (Author abstract) (22 Refs)

32. EVIDENCE FOR SIMIAN VIRUS 40 LATE TRANSCRIPTIONAL CONTROL: MIXED INFECTIONS OF WILD-TYPE SIMIAN VIRUS 40 AND A LATE LEADER DELETION MUTANT EXHIBIT TRANS EFFECTS ON LATE VIRAL RNA SYNTHESIS.

Alwine JC
Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Virol; 42(3):798-803 1982

Mixed infections involving equal multiplicities of wild-type simian virus 40 and viable deletion mutant dl861 resulted in decreased cytoplasmic levels of wild-type-derived late mRNA, as well as very low to undetectable levels of mutant-derived late mRNA, as compared with individual infections. The dl861 deletion removes 16 to 25 base pairs from the late leader region. This deletion was shown to be the direct cause of the mixed-infection effect; replacement of the deletion with wild-type sequences restored normal levels of late mRNAs in mixed infections. Other viral functions, eg, early gene expression and replication, were found to be unaffected by the dl861 deletion. Further examination of the mixed-infection effect showed that the levels of unspliced nuclear precursors of late mRNA, derived from both the mutant and wild-type genomes, were decreased or undetectable, in accord with the cytoplasmic results. Thus, the effect appears to be occurring at the transcriptional level. These data demonstrate a trans-acting effect on late transcription, which is detectable due to the presence of the dl861 mutant in the mixed infection. This finding is indicative of a diffusible factor which exerts a control on simian virus 40 late gene expression at the transcriptional level. A model for positive control of simian virus 40 late gene expression is presented. (Author abstract) (14 Refs)

33. MUTANT OF SIMIAN VIRUS 40 LARGE T-ANTIGEN THAT IS DEFECTIVE FOR VIRAL DNA SYNTHESIS, BUT COMPETENT FOR TRANSFORMATION OF CULTURED RAT CELLS.

Stringer JR
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
J Virol; 42(3):854-864 1982

A mutant was isolated which demonstrates that the transforming activity of simian virus 40 large T-antigen is separable from its function in viral DNA replication. The mutant, SVR9D, is nonconditionally defective for viral DNA synthesis, but competent at wild-type level for morphological transformation of cultured rat cells. The lytic growth defect in SVR9D is complemented by the simian virus 40 A gene product present in the transformed CV1 cell line, COS1. The lesion in SVR9D DNA was mapped genetically by marker rescue of plaque formation and localized to a 214-base-pair segment of the viral genome bounded by nucleotide numbers 4100 and 4314. DNA sequence analysis showed the mutation to be an adenine-to-guanine transition at nucleotide number 4178. This change predicts a lysine-to-glutamic acid amino acid change at residue number 214 of the mutant large T-antigen polypeptide. (Author abstract) (32 Refs)

34. EXPRESSION OF TRANSDUCED GENES IN MAMMALIAN CELLS (MEETING ABSTRACT)

Berg P

Department of Biochemistry, Stanford University Medical Center, Stanford, CA

Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Our laboratory has explored two approaches to achieving transduction-transformation of mammalian cells. One uses recombinants constructed in vitro from suitably modified cloned cDNAs or prokaryote and eukaryote-derived genomic segments and SV40 DNA from which segments encoding early and late viral functions have been excised. In this experimental design, the recombinant viral genomes must contain the origin of SV40 DNA replication and must not be larger than 5.3 kb in order to be propagated as mature virion genomes; moreover, since the recombinant genomes are defective, propagation can occur only with a helper virus to provide the missing gene product(s). A virtue of this approach is that amplification of the recombinant genomes ensures a high yield of the mRNAs and proteins expressed from the transduced genes. The second approach exploits a new group of transducing-transforming DNA vectors for the introduction and maintenance of new genes in a variety of mammalian cells. One prototype of this class of vectors, pSV2-neo, developed by Peter Southern and Bruce Howard, contains a DNA segment from the plasmid pBR322, in order to permit propagation of the recombinants in Escherichia coli, and a transcription unit comprising the SV40 early region promoter, the dominant selectable marker, Econeo, an intervening sequence, and a poly A site. Cells transformed with pSV2-neo (frequency, 10(-4) to 10(-5)) grow in media containing the inhibiting aminoglycoside G418. Unique restriction sites in pSV2-neo DNA permit the introduction of other, nonselectable genes into the same vector and, thereby, the cotransformation of cells for these otherwise nonselectable phenotypes. (no Refs)

35. POLYOMA-LIKE PARTICLE: CHARACTERIZATION OF THE DNA ENCAPSIDATED IN VITRO BY POLYOMA EMPTY CAPSIDS.

Slilaty SN, Berns KL, Aposhian HV

Dept. Cellular and Developmental Biology, Univ. Arizona, Tucson, AZ, 85721

J Biol Chem; 257(11):6571-6575 1982

Polyoma empty capsids and DNA interact in a cell-free system to form a polyoma-like particle (PLP). The particle is stable in high concentrations of salt and contains a DNA fragment that is protected by the capsid from the action of DNase I. The DNA extracted from PLP is heterogeneous in size. It has a mean mol wt of 1.2 x 10(6) with a standard deviation of +-0.5 x 10(6). Analysis of PLP DNA with restriction endonucleases and the Southern blot technique reveals that a specific primary sequence is not required for PLP formation. Either linear, circular, or supercoiled polyoma DNA, as well as single-stranded DNA, rRNA, and the synthetic homopolymers poly(dA)-poly(dT) and poly(dG)-poly(dC) can be used for PLP formation. It is concluded that polyoma empty capsids can be used to bind and encapsidate nucleic acids differing in their primary, secondary, and superhelical tertiary structure to form, in vitro, stable polyoma-like particles. (Author abstract) (28 Refs)

36. THE COMPLETE NUCLEOTIDE SEQUENCE OF POLYOMA VIRUS AND IDENTIFICATION OF THE TRANSFORMING (CARCINOGENIC) GENES.

Soeda E
Natl. Inst. Genetics, Mishima, Shizuoka Prefecture 411, Japan
Nippon Nogeikagaku Kaishi; 56(1):31-37 1982

The polyoma virus is a small-type tumorigenic virus composed of a circular double strand DNA of 5,292 bases. The complete nucleotide sequence of the polyoma virus is described, and the mechanism of carcinogenesis of cells by the virus is clarified. Genetic analysis of the mutated region of wild and non-transformed strains of N18 is performed, and differences between the patterns of carcinogenesis of other papovaviruses (SV40, BKV, etc) and that of the polyoma virus are discussed. (39 Refs) (In JPN)

37. CARBOXY TERMINUS OF POLYOMA MIDDLE-SIZED TUMOR ANTIGEN IS REQUIRED FOR ATTACHMENT TO MEMBRANES, ASSOCIATED PROTEIN KINASE ACTIVITIES, AND CELL TRANSFORMATION.

Carmichael GG, Schaffhausen BS, Dorsky DI, Oliver DB, Benjamin TL
Dept. Microbiology, Univ. Connecticut, Sch. Medicine, Farmington, CT, 06032
Proc Natl Acad Sci USA; 79(11):3579-3583 1982

We have constructed a transformation-defective polyoma virus mutant (Py 1387-T) that directs the synthesis of a normal small tumor antigen, a functional large tumor antigen, and a truncated (51,000-dalton) middle-sized tumor (mT) antigen that lacks 37 amino acids at its COOH terminus. The shortened mT polypeptide is missing the hydrophobic 'tail' thought to be responsible for the anchorage of this protein into the plasma membrane and is in fact in cytosol fractions. This truncated mT polypeptide is inactive in an in vitro protein kinase assay and is altered in its phosphorylation in vivo. Mutant 1387-T differs from wild-type virus in having a T-A base pair instead of a C-G base pair at nucleotide position 1387. This change was introduced into viral DNA by using a synthetic undecanucleotide as a specific mutagen. Wild-type polyoma DNA was rendered single stranded by molecular cloning into coliphage M13. The oligonucleotide, which hybridizes with a mismatch at the site to be altered, was used to prime the synthesis of double-stranded closed circular DNA. Progeny recombinant phages were screened by DNA sequence analysis for the desired base change. The polyoma mutant was reconstructed from recombinant phage replicative form DNA molecules containing the mutation. (Author abstract) (45 Refs)

38. CHANGE OF DNA NEAR THE ORIGIN OF REPLICATION ENHANCES THE TRANSFORMING CAPACITY OF HUMAN PAPOVAVIRUS BK.

Watanabe S, Yoshiike K
Dept. Enteroviruses, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan
J Virol; 42(3):978-985 1982

A turbid-plaque-forming mutant (pm522) of human papovavirus BK, which has a small deletion at about 0.7 map unit and grows somewhat more slowly in human cells than does wild-type BK virus, transformed hamster and rat cells in culture much more efficiently than did wild-type virus. Another plaque morphology mutant, pm525, forming turbid plaques larger than those of pm522 also had a high transforming capacity. The similar difference in transforming capability between wild-type and plaque morphology viruses was observed with DNAs extracted from virions. Recombinant viruses were constructed from the wild-type DNA fragment lacking HindIII-C (0.62 to 0.73 map unit) and pm522 HindIII-C (including the origin of replication) by the molecular cloning method. Characterization of the recombinants showed that the change near the origin of DNA replication was responsible both for the altered plaque morphology and for the enhanced transforming capacity of the BK virus mutant. (Author abstract) (33 Refs)

39. COMPLEMENTATION FOR REPLICATIVE FORM DNA REPLICATION OF A DELETION MUTANT OF H-1 BY VARIOUS PARVOVIRUSES.

Rhode SL
Inst. Medical Res. Bennington, Bennington, VT, 05201
J Virol; 42(3):1118-1122 1982

A defective interfering genome of the parvovirus H-1 called dl1, has been isolated and characterized. The only alteration in dl1 that has been detected is a 300-base-pair deletion at map position 38. Replicative form DNA replication of dl1 requires the RF rep function of a helper virus and the parvoviruses H-1, H-3, MVM, or MVM(i), but not LuIII complement dl1 for replicative form DNA replication. (Author abstract) (8 Refs)

IMMUNOLOGICAL STUDIES

40. ANALYSIS OF DR-LIKE MOLECULES ON A MARMOSET EPSTEIN-BARR VIRUS-INDUCED CELL LINE USING A MONOMORPHIC ANTI-HUMAN HLA-DR MONOCLONAL ANTIBODY.

Teillaud JL, Charron D, Goujet-Zalc C, Mahouy G
Institut de Recherches sur les Maladies du Sang, Hopital Saint-Louis, F-75475 Paris Cedex 10, France
Eur J Immunol; 12(5):446-448 1982

Mouse anti-HLA D region-related (DR) monoclonal antibodies have been found to cross-react with peripheral blood leukocytes from one primate species, the common marmoset (Callithrix jacchus). Immunoprecipitates of radioactively labeled cells extracted from a marmoset Epstein-Barr virus-induced cell line were analyzed by one- and two-dimensional gel electrophoresis and compared with the DR antigens of a human lymphoblastoid B cell line. Two chains of estimated molecular weights of 34,000 (alpha) and 28,000 (beta), similar to the human alpha and beta chains, have been observed in marmoset immunoprecipitates. Additionally, a set of spots located in the same area as the set of invariant spots found in human HLA-DR antigens is shown by two-dimensional gel electrophoresis. Thus, cross-reacting anti-human HLA-DR monoclonal antibodies could be used to analyze the expression and the structure of marmoset DR-like antigens. (Author abstract) (19 Refs)

41. EPSTEIN-BARR VIRUS-SPECIFIC CYTOTOXIC T-CELL CLONES RESTRICTED THROUGH A SINGLE HLA ANTIGEN.

Wallace LE, Rickinson AB, Rowe M, Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England
Nature; 297(5865):413-415 1982

Epstein-Barr (EB) virus-specific human cytotoxic T-cell clones, recognizing the virus-induced lymphocyte-detected membrane antigen (LYDMA) in association with one particular human leukocyte antigen (HLA)-A or -B determinant, were established in vitro. T-cells were prepared by in vitro reactivation from seropositive donor SW (HLA-A11, AW24, B7, and BW35) cells. Strong killing of the autologous cell line was not accompanied by any significant reactivity against EB virus genome-negative human leukemic cell lines HSB2 and K562, which were included as indicators of natural killer-like activity. Lysis of allogeneic EB virus-transformed cells was particularly strong when associated with either HLA-A11 or BW35 antigen matching, and progressively weaker with matching through B7 and AW24. Samples of effector cells were cloned and analyzed. Tests with clone C2 suggested specificity for the viral antigen LYDMA in association with HLA-A11. Clone C2 killed 8/8 EB virus-transformed cell lines from donors typed HLA-A11, but did not kill any of 15 corresponding lines from A11-negative donors. No lysis of EB virus genome-negative target cells was observed. Clone G13 and H8 showed similar results, while clone G9 gave a different pattern of reactivity, suggesting specific recognition of LYDMA in association with HLA-BW35. Clone G9 killed 9/10 EB virus-transformed target cell lines from donors typed HLA-BW35 but none of the 11 corresponding lines tested from BW35-negative donors or any of the relevant EB virus genome-negative target cells. The mechanisms for the observed reactivities are discussed. (24 Refs)

42. A MONOCLONAL ANTIBODY WITH ANTI-BURKITT LYMPHOMA SPECIFICITY. I. ANALYSIS OF HUMAN HAEMATOPOIETIC AND LYMPHOID CELL LINES.

Wiels J, Lenoir GM, Fellous M, Lipinski M, Salomon JC, Tetaud C, Tursz T
Laboratoire d'Immunologie Clinique, Institut G. Roussy, Rue C. Desmoulins, 94800 Villejuif, France
Int J Cancer; 29(6):653-658 1982

There is a hybridoma-produced monoclonal rat IgM (38-13) which appears to define a Burkitt's lymphoma-associated antigen (BLA). In this paper, we describe the reactivity of 38-13 with a panel of human hematopoietic and lymphoid cell lines. In indirect immunofluorescence (IF) assays, 15 of 26 Burkitt's lymphoma (BL) lines studied were clearly stained with 38-13 (from 13 to 100% positive cells) by microscope, with varying numbers of heavily labeled cells. In these positive cell lines, fluorescence-activated cell-sorter (FACS) analysis demonstrated that BLA was actually present on all the cells. Positive BL included Epstein-Barr virus (EBV) genome-carrying lines and EBV-negative ones; thus, BLA is not related to the presence of EBV. Most of the 15 BL cells that reacted with 38-13 contained a typical t(8;14) translocation, but had variant translocations such as t(2;8) and t(8;22). The cells were derived from BL patients of different geographical origins and clinical features. Four BL lines were poorly stained and seven were negative with 38-13 in IF assays. The 32 EBV-positive lymphoblastoid cell-lines (LCL) studied were negative. In three line pairs, consisting of a tumor line and an LCL from the same patient, only the BL line was demonstrated to react with 38-13. A series of non-BL cells, including hematopoietic, lymphoid and solid tumor lines, all failed to react with 38-13. Various attempts to modulate the expression of BLA on BL cells were unsuccessful. However, it cannot be ruled out that BLA is actually a transient B-cell differentiation marker. (Author abstract) (18 Refs)

43. EPSTEIN-BARR VIRUS (EBV)-LYMPHOID CELL INTERACTIONS. II. THE INFLUENCE OF THE EBV REPLICATION CYCLE ON NATURAL KILLING AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AGAINST EBV-INFECTED CELLS.

Patel PC, Menezes J
(c/o Menezes) Lab. Immunovirology, Sainte-Justine Hosp., 3175 Chemin Cote Sainte-Catherine, Montreal, Quebec H3T 1C5, Canada
Clin Exp Immunol; 48(3):589-601 1982

We investigated the influence of the Epstein-Barr virus (EBV) replication cycle on natural killing (NK) activity and antibody-dependent cellular cytotoxicity (ADCC) against EBV-infected cells. Peripheral blood lymphocytes from healthy EBV-seropositive and -seronegative donors were separated on Ficoll-Hypaque gradients and used as effector cells in the standard 51Cr release assay to measure NK and ADCC. EBV-genome positive RAJI and DAUDI cells superinfected with either the non-transforming P3HR-1 EBV or the transforming B95-8 EBV were used as targets. The results obtained show that most normal individuals have ADCC and NK activity against P3HR-1 EBV-infected RAJI cells. Both the cytotoxic activities increased with the proportional increase in effector/target (E/T) ratios, assay incubation time, dose of the infecting virus and the time of pre-infection with EBV. Moreover, the data obtained indicate that different immune mechanisms are effective at different stages of the virus replication cycle. During the early stages of virus replication, EBV-superinfected cells are more susceptible to ADCC than to NK, whereas in later stages the susceptibility to NK is increased significantly and appears to play a more dominant role. The nature of the target cells or the strain of EBV used to superinfect these targets did not influence their susceptibility to ADCC and NK activity; however some quantitative differences were found. Using metabolic inhibitors such as cytosine arabinoside, phosphonoacetic acid, actinomycin D, cycloheximide and puromycin, it was found that new DNA synthesis is not essential but some RNA and protein synthesis is necessary, late in the viral cycle, for the superinfected cells to become susceptible to NK and ADCC. (Author abstract) (34 Refs)

44. MOLECULAR INTERACTIONS IN HUMAN T-CELL-MEDIATED CYTOTOXICITY TO EPSTEIN-BARR VIRUS. I. BLOCKING OF EFFECTOR CELL FUNCTION BY MONOCLONAL ANTIBODY OKT3.

Tsoukas CD, Fox RI, Carson DA, Fong S, Vaughan JH
Dept. Clinical Res., Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Cell Immunol; 69(1):113-121 1982

The ability of different anti-human T-cell lymphocyte monoclonal antibodies to inhibit the effector function of the cytotoxic T-cell response against autologous Epstein-Barr virus (EBV)-infected B-cell targets has been tested. It was found that monoclonal antibody, OKT3, which reacts with most human T cells, blocks the effector cell function in the absence of complement, an effect that was dose dependent. When monoclonal antibody OKT3 was tested at a concentration of 1 ug/ml, inhibition of cytotoxicity ranged between 50 and 80%. The F(ab')2 fragment of OKT3 inhibited as well as the intact IgG molecule, indicating that the Fc portion of the antibody is not necessary for the cytotoxicity blocking. The Fab fragment of OKT3 had lower blocking activity per microgram of protein tested. Antibodies SC1, OKT11 (anti-pan T cell), OKT8 (anti-cytotoxic/suppressor subset), and L368 (anti-HLA) did not have any discernable blocking effects. However, antibodies SC1, OKT8 and L368 could abrogate the cytotoxic activity in the presence of complement. Blocking by OKT3 was not due to its being present on the cell surface in higher concentrations than the other monoclonal antibodies since cytofluorographic analysis demonstrated that the amount of OKT8 or L368 antibodies bound on the cells was greater than OKT3. In addition, blocking was not due to antigenic modulation since incubation with antibody OKT3-F(ab')2 was not associated with a significant decrease in the amount of its reactive antigen. Under the conditions tested OKT3 did not affect cell viability or cause agglutination. (Author abstract) (34 Refs)

45. INDUCTION OF MARMOSET CELLULAR CYTOTOXICITY TO AUTOLOGOUS EBV-TRANSFORMED LYMPHOBLASTOID CELL LINES (MEETING ABSTRACT)

Abb J, Deinhardt F

No affiliation given

10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

Marmosets have proven particularly useful as animal models for viral oncogenesis. Experimental infection of these small New World primates with Epstein-Barr virus (EBV) leads to the development of lymphomas or lymphocytic leukemias. Transformation of marmoset peripheral blood lymphocytes (PBL) with EBV in vitro allows the establishment of permanent lymphoblastoid cell lines (LCL) with B-cell characteristics. Studies of the immune response of marmosets in vitro to EBV-associated antigens expressed on autologous LCL have shown that cell-mediated cytotoxicity could not be induced in conventional mixed lymphocyte-LCL cultures (MLLC). Cytotoxic effector cells to autologous marmoset EBV-LCL, however, were induced by the addition of third party allogeneic or xenogeneic lymphocytes to marmoset PBL and autologous EBV-LCL in vitro. The induced cytotoxic lymphocytes had the morphological and functional characteristics of natural killer (NK) cells: Marmoset effector cells were nonadherent and possessed receptors for Fc-IgG; effector cells showed no restriction for antigens of the major histocompatibility complex (MHC) or EBV-genome positive target cells; effector cell activity appeared to be regulated by the endogenous production of interferon (IF) in third party MLLC. Further evidence for the regulatory role of IF was provided by the observation that lymphocyte cytotoxicity to autologous EBV-LCL could also be induced by incubation of marmoset PBL with partially purified human leukocyte IF or with IF inducers (lectin mitogens, poly I:C). Addition of antiserum to human leukocyte IF to third party MLLC inhibited the induction of cell-mediated cytotoxicity to autologous marmoset EBV-LCL. (no Refs)

46. IMMUNOLOGICAL DEFECT IN A FAMILY WITH MULTIPLE NASOPHARYNGEAL CARCINOMA AND BURKITTS' LYMPHOMA (MEETING ABSTRACT)

Joncas J, Seeley J, Purtilo D, Ghibu FM, Lichaa H, Robillard L, Rioux E

No affiliation given

10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

A Canadian family of 15 members, 3 of whom died of nasopharyngeal carcinoma (2) and Burkitt's lymphoma (1), was investigated for immunological defects. The diagnosis made during the life of these patients was confirmed in retrospect by examination of the pathological slides by three different pathologists. A presumptive association with the Epstein-Barr virus (EBV) was supported by very high EBV antibody titers on stored sera from these patients. All the family members were EBV antibody (VCA, viral capsid antigen and EBNA, nuclear antigen) positive but EA (early antigen) antibody negative except the patients with tumors (titers up to 320) and the mother (titer of 10). The occurrence of a plasmacytoma in a maternal first degree cousin and low serum IgA values in another first degree cousin and two of the family members prompted us to follow-up this family and investigate its members further immunologically. The mother who had normal Ig levels in 1975 now has marked hypogammaglobulinemia and has a relatively much higher EBV-VCA antibody titer than any other members of the family. The living family members except 3 male members have abnormally high numbers of T4 (helper) lymphocytes. These and other findings as well as the characteristics of the cell lines established from members of this family suggest a primary B cell dysfunction. The anomaly noted in T cell subpopulations is possibly secondary to the B cell dysfunction but may contribute to B cell proliferation and neoplastic transformation eventually. (1 Ref)

47. NEUTRALIZING ANTIBODY TO HERPES SIMPLEX VIRUS TYPE 1 IN PATIENTS WITH ORAL CANCER.

Shillitoe EJ, Greenspan D, Greenspan JS, Hansen LS, Silverman S

Univ. California, San Fracisco, CA, 94143

Cancer; 49(11):2315-2320 1982

Neutralizing antibody to Herpes simplex virus type 1 (HSV-1), type 2, and measles virus was measured in the serum of patients with oral cancer, patients with oral leukoplakia, and in control subjects who were smokers and nonsmokers. Significantly higher titers to HSV-1 were found in controls who smoked than in controls who did not smoke. Patients with untreated oral cancer had HSV-1 neutralizing titers similar to those of the controls who smoked, but those with later stage tumors had higher titers than those with earlier stage tumors. In patients who were tumor free after treatment for oral cancer, higher antibody titers to HSV-1 were associated with longer survival times. No association was found between clinical status and antibody to measles virus. The data are consistent with a role for both HSV-1 and smoking in the pathogenesis of oral cancer. (Author abstract) (26 Refs)

48. LOCAL IMMUNITY IN PATIENTS WITH HERPES GENITALIS (CLINICAL AND ELECTRON MICROSCOPE STUDY).

Kalamkarian AA, Delektorskii VV, Grebeniuk VN, Masiukova SA, Zakhaleva VA
Dept. Dermatology, Central Res. Inst. Skin-Venereal Diseases, Moscow, USSR
Vestn Dermatol Venerol; (4):4-7 1982

The state of local immunity was studied in 20 patients (17 men, 3 women) with recurrent herpes genitalis (HG). Electron microscope examination of vesicle specimens showed intracellular and extracellular localization of mature virions. Insufficient antiviral resistance was associated with incomplete phagocytosis of herpes simplex virus by macrophages. (26 Refs) (In RUS)

49. IN-VITRO-INDUCED HUMAN T CELLS CYTOTOXIC AGAINST HERPES-SIMPLEX-VIRUS-INFECTED TARGETS: MODULATION BY THEOPHYLLINE OF THE INDUCTION AND EFFECTOR STAGES.

Rola-Pleszczynski M, Lieu H
Div. Immunology, Dept. Pediatrics, Faculte de Medicine, Universite de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada
Immunopharmacology; 4(3):225-233 1982

Effect of short vs prolonged exposure of human peripheral blood mononuclear leukocytes (PBML) to theophylline (TH) on their subsequent cytotoxic capacity was studied. PBML subpopulations were also studied to assess their respective participation in the phenomenon. Blood donors were healthy adult volunteers with a negative history for herpes labialis or genitalis. The positively selected Tgamma subset of T cells was slightly, but significantly, more susceptible to TH than was the THr subpopulation. Cytotoxicity against the infected and uninfected targets was similarly affected by TH, when effectors were either unfractionated PBML or THr cells. Similar depression of final cytotoxic activity was observed whether TH was used during sensitization only or during the cytotoxic assay. No greater impairment of cytotoxicity was seen when PBML were left in contact with the drug throughout both stages. A 30-min preincubation with TH increased the proportion of Tgamma cells after 3 days of sensitization but failed to modify significantly the proportions of the other cell subsets at 3 or 6 days. A 60-min preincubation, however, was accompanied by a significant increase in proportion of Tgamma cells at 3 and 6 days of sensitization and of THr cells at 6 days. The enhancing effect of a 1-hr preincubation with TH on subsequent third-day cytotoxicity against herpes simplex virus-infected target cells is presented. Results indicated that the THr T-cell subset fractionated after sensitization was least affected by the presence of TH during the sensitization phase and that a short preincubation with TH had an enhancing, rather than a depressive, effect on Tgamma and THr cells at the end of a 3-and 6-day period of sensitization. (17 Refs)

50. ANTIBODIES TO ADULT T-CELL LEUKEMIA-VIRUS-ASSOCIATED ANTIGEN (ATLA) IN SERA FROM PATIENTS WITH ATL AND CONTROLS IN JAPAN: A NATION-WIDE SERO-EPIDEMIOLOGIC STUDY.

Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, Kikuchi M, Ichimaru M, Yunoki K, Sato I, Matsuo R, Takiuchi Y, Uchino H, Hanaoka M
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Int J Cancer; 29(6):631-635 1982

A nation-wide sero-epidemiologic survey of adult T-cell leukemia virus (ATLV), detected as anti-ATLA (ATLV-associated antigen), was made in Japan. Sera from adult donors in 15 different locations were screened for anti-ATLA. High incidences (6 to 37%) of antibody-positive donors were found in seven regions, one in northern Japan, and the others in southwestern regions. These areas are ATLV-endemic areas corresponding to ATL-endemic areas. Examination of sera from healthy donors aged 6 to 80 yr in ATL-endemic areas showed an age-dependent increase of seropositive donors with a maximum of about 30% to 40 yr of age. Anti-ATLA was found in all but two of 142 patients with ATL. Anti-ATLA-positive patients with ATL were mainly found in ATLV-endemic areas and only a few in ATL-nonendemic areas. Six patients with cutaneous T-cell lymphoma in ATLV-nonendemic areas gave a negative reaction for anti-ATLA. The geometric mean titer of anti-ATLA of patients with ATL was higher than that of healthy donors. (Author abstract) (9 Refs)

51. GROUPING OF HUMAN ADENOVIRUSES BY EARLY ANTIGEN REACTIVITY.

Gerna G, Cattaneo E, Revello MG, Battaglia M
Virus Lab., Inst. Infectious Diseases, Univ. Pavia, 27100 Pavia, Italy
J Infect Dis; 145(5):678-682 1982

Prototype strains of human adenovirus (AV) (serotypes 1-35) as well as 49 wild strains were studied for reactivity of early antigens (EAs) with type-specific rabbit immune sera, using the immunoperoxidase antibody technique for determination of virus-specific IgG. The EAs of all AV serotypes belonging to one group reacted strongly with all type-specific immune sera of the homologous group. Reactivity with antisera to heterologous groups was moderate or absent except for the EAs of AV Type 4, which reacted strongly with all AV-immune sera. Thus, on the basis of EA reactivity, all AV strains appeared to fall into five distinct groups (corresponding to DNA homology groups): Group A, Types 12, 18, and 31; Group B, Types 3, 7, 11, 14, 16, 21, 34, and 35; Group C, Types 1, 2, 5, and 6; Group D, Types 8-10, 13, 15, 17, 19, 20, 22-30, 32, and 33; and Group E, Type 4. For diagnostic virology, EA grouping is a valid alternative to differential hemagglutination; it is more complete, and all AV strains can be rapidly classified. (Author abstract) (15 Refs)

52. IMMUNOCOMPETENCE AND MALIGNANCY.

Melief CJ, Schwartz RS
Hematology Service, New England Medical Center Hosp., Boston, MA
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Present concepts regarding immunocompetence and malignancy are reviewed. The general applicability of the theory of immunological surveillance to the pathogenesis of cancer is questioned. Immunological surveillance arguments fail to acknowledge the parallel system of adaptive immunity - blocking antibody - which protects the tumor against the cell-mediated immunity of the host. The virulent virus strains that are used to demonstrate immunosuppression by oncogenic viruses are not considered to have any relevance to malignancies as they develop naturally. The issue of defense mechanisms against oncogenic viruses through infectious agents must be separated from that of the defense against the cells they have transformed to a malignant state. In nearly all studies designed to determine the subject's ability to respond to antigens of his own neoplasm, evidence for cell-mediated immunity against antigens of the tumor (either from the patient or from a histologically similar allogenic tumor) has been found. Two experimental models are consistent with the notion that unrestrained proliferative activity of lymphoid tissue can culminate in neoplasia: persistent antigenic stimulation combined with partial immunosuppression and chronic graft vs host reactions. Recent experimental results now permit a serious examination of the notion that the immune reaction stimulates the growth of tumors. (267 Refs)

53. A STUDY OF THE RELATIONSHIP BETWEEN THE PROGNOSIS OF CHRONIC ACTIVE HEPATITIS AND THE HBV ASSOCIATED ANTIGEN/ANTIBODY SYSTEMS (MEETING ABSTRACT)

Takase K, Tameda Y, Kosaka Y

First Department of Medicine, Mie University Hospital, Tsu, Japan

Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Our series consisted of 31 patients admitted to our clinic and diagnosed as chronic active hepatitis (CAH) over the period of 12 years from January 1, 1969 until December 31, 1980. The diagnosis was based on liver histology in all these patients, who were then followed up with liver biopsy performed subsequently at an interval of more than a year. Determination were made by RIA (radioimmunoassay) methods of HBsAg, anti-HBs, HBeAg, anti-HBe anti-HBc in blood serum taken from each patient on initial and final liver biopsy. The serum specimen were kept frozen at-20C until time of use. An attempt was made to examine the relationship between the HBV (hepatitis B virus)-associated antigen/antibody systems so determined and the prognosis of chronic hepatitis based on follow-up liver biopsy. On initial liver biopsy 5 of 13 patients with CAH with spotty or focal necrosis were HBsAg positive, as 5 of 7 patients with sublobular necrosis and 7 of 11 patients with lobular disorganization. Most of HBsAg negative patients were anti-HBs or anti-HBc positive: HBV-associated antigen or antibody was completely undetectable in only 4 of these 31 patients. There was no difference in the frequency of progression to liver cirrhosis (LC) between 17 HBsAg positive patients with CAH. On the other hand, progression to LC occurred in only 1 of 8 HBeAg negative patients, compared to 5 of 10 HBeAg positive patients, who were HBsAg positive. There were 5 patients who were HBeAg positive initially but then become HBeAg negative in the course of observation. (no Refs)

54. DETECTION OF ANTI-HBC (HEPATITIS B CORE ANTIBODIES) AND ITS CLINICAL SIGNIFICANCE.

Wang Q, Shi X, Wang D, Chou D, Yang Y, Zhang X, Jiang W, Chen H, Xu C, Zou W

Dept. Infectious Diseases, Affiliated Ruijin Hosp., Shanghai Second Medical Coll., Shanghai, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(3):194-197 1981

Using partially purified hepatitis B core antigen, the anti-HBc was analyzed in 202 normal subjects and 600 patients including 424 with various types of hepatitis, 145 symptomless HBsAg carriers, 8 with liver cirrhosis and 23 with liver cancer. Results showed that highest infection rate of hepatitis B virus (HBV) occurred in the hepatitis patients (67.2-99%), while in patients with liver cirrhosis and liver cancer the HBV infection rates were 75% and 56.6% respectively, as compared to 8.4% in normal subjects. (11 Refs) (In CHI)

55. CLINICAL AND IMMUNOLOGICAL ASPECTS OF HEPATITIS B VIRUS INFECTION IN CHILDREN WITH HAEMATOLOGICAL MALIGNANCIES.

Koscielniak E

Dept. Hematology, Pediatric Clinic, Medical Acad., Wronskiego 11, 50-372 Wroclaw, Poland

Arch Immunol Ther Exp (Warsz); 29(5):689-695 1981

One hundred forty three patients with hematological malignancies were screened at the onset and during the disease for hepatitis B surface antigen (HBsAg) in the serum. HBsAg was found in serum of 38/143 patients (26.5%) in a mean period of 14.5 mo after the diagnosis was established. The relationship between immunological status of the patients and the course of the infection was analyzed. In 17/38 patients who developed icteric hepatitis, the mean amounts of E-rosetting lymphocytes were significantly higher than in the anicteric hepatitis group and asymptomatic HBsAg carriers. These two groups of patients showed a tendency to persistence of HBsAg and developing of chronic carrier state or chronic hepatitis. (Author abstract) (19 Refs)

56. HEPATITIS B E ANTIGEN AND ANTIBODY TO HEPATITIS B E ANTIGEN IN THE PATIENTS WITH PRIMARY HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT)

Fukuda Y

2nd Department of Internal Medicine, Kyoto University School of Medicine, Kyoto, Japan

Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

A close association between heptitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC) has been noted. Therefore, to gain further insight into this relationship, we undertook the present study. First, we looked for the prevalence of HBeAg and antibody to HBeAg (HBeAb) in the patients with HCC and compared the results in asymptomatic carrier (ASC), chronic hepatitis (CH) and liver cirrhosis (LC). Second, the serial detection of HBeAg/HBeAb system was done retrospectively in the sera from the patients who were HBsAg-positive chronic liver disease and progressed to HCC. Sera of 73 patients with HBsAg-positive HCC were tested for HBeAg and HBeAb. HCC was diagnosed histologically either by liver biopsy or autopsy, or by increased alpha-fetoprotein (AFP) levels, liver scan, CT (computed tomography) scan, and celiac angiography. The control consisted of 76 patients with ASC, 101 patients with CH and 50 patients with LC. Twenty six of 73 (36%) patients with HCC were positive for HBeAg and 25 (34%) were positive for HBeAb. Positive frequency of HBeAg in the patients with ASC, CH and LC were 29%, 48% and 50% respectively. We have done the retrospective determination of HBeAg and HBeAb in sera from 11 patients with HCC who were followed as liver cirrhosis for more than 3 years. Nine of 11 patients showed persistent HBeAg-positive state throughout their clinical course and 2 of 11 showed persistent HBeAg-positive state until about 1.5 years and 2 months before occurrence of HCC respectively. (no Refs)

57. DEMONSTRATION OF PAPILLOMAVIRUS ANTIGEN IN PARAFFIN SECTIONS OF LARYNGEAL PAPILLOMAS.

Braun L, Kashima H, Eggleston J, Shah K
Dept. Pathobiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, 615 North Wolfe St., Baltimore, MD, 21205
Laryngoscope; 92(6,part1):640-643 1982

A papillomavirus antigen has been identified in tissue sections of laryngeal papillomata removed at endoscopic operations. The demonstration of the papillomavirus antigen was achieved using the peroxidase-antiperoxidase test of Sternberger after a broadly cross-reactive rabbit antiserum to the papillomavirus capsid antigen was incubated with the tissue sections. The antigen was detected in specimens from 7 of 15 patients with juvenile-onset laryngeal papillomas, but could not be demonstrated in the specimens from six patients with adult-onset papillomas. In all, 73 biopsy specimens from 21 patients were selected for study; 18% (11/61) of the sections from the juvenile-onset patients and 0% (0/12) of the sections from the adult-onset patient specimens exhibited the papillomavirus antigen. The presence of the virus antigen did not correlate with the stage of disease, nor with the duration or severity of the illness. The implications of the findings are discussed. (Author abstract) (17 Refs)

58. FREQUENCY AND DISTRIBUTION OF PAPILLOMAVIRUS STRUCTURAL ANTIGENS IN VERRUCAE, MULTIPLE PAPILLOMAS, AND CONDYLOMATA OF THE ORAL CAVITY.

Jenson AB, Lancaster WD, Hartmann DP, Shaffer EL
Dept. Pathology, Georgetown Univ., Sch. Medicine and Dentistry, Washington, DC, 20007
Am J Pathol; 107(2):212-218 1982

Sixty-seven proliferous squamous epithelial lesions of the oral cavity were examined for the presence of human papillomavirus whole (structural) virion antigens by a peroxidase-antiperoxidase technique having immunospecificity against genus-specific (common) antigens of the papillomaviruses. A positive reaction for papillomavirus genus specific antigens was found in 18 of 29 verrucae, 2 of 5 multiple papillomas, and 3 of 5 condylomata; common antigens were not detected in 28 keratoacanthomas. The positive reaction was invariably intranuclear in cells having a focal or diffuse distribution in the superficial epithelium. This study shows that a variety of squamous epithelial lesions of the mucosa are associated with human papillomaviruses and suggests that these viruses may play an important role in the etiology of some cases of squamous hyperplasia of the oral cavity. (Author abstract) (24 Refs)

59. FREQUENCY AND DISTRIBUTION OF PAPILLOMAVIRUS ANTIGENS IN CERVICAL DYSPLASIA AND CARCINOMA IN SITU (MEETING ABSTRACT)

Kurman RJ, Lancaster WD, Jenson AB
Department of Pathology and Obstetrics and Gynecology, Georgetown University Hospital, Washington, DC
Lab Invest; 46(1):46A 1982

Two hundred and ninety-three cases of cervical dysplasia (139 mild, 72 moderate, 44 severe) and carcinoma in situ (CIS) (38) retrieved from the surgical pathology files of Georgetown University Hospital from 1974 to 1977, were screened for the presence of papillomavirus (PV) antigens, using a peroxidase-antiperoxidase technique, having immunospecificity against the genus-specific (common) antigens of the papillomaviruses on formalin-fixed paraffin-embedded tissue. A positive reaction for PV antigens was found in 68 mild dysplasias, 13 moderate dysplasias, six severe dysplasias, and three CIS. Positive cells were focally or less commonly diffusely distributed in the superficial and intermediate layers of the epithelium in areas of mild or moderate dysplasia and also associated with or immediately adjacent to areas of severe dysplasia and CIS. The positive reaction, invariably intranuclear, was present in nuclei with wrinkled nuclear membranes that were rounded, ovoid, or flattened. Positive cells with flat or ovoid nuclei were mononuclear with scant cytoplasm, whereas those with rounded nuclei were sometimes binucleate and characteristically contained clear cytoplasm. Cells with similar morphologic features to those showing a positive reaction of PV antigens were frequently negative but were also considered as showing wart virus atypia. Cells showing wart virus atypia, irrespective of being PV-positive or negative, were found in 126 mild dysplasias, 51 moderate dysplasias, 24 severe dysplasias, and 10 CIS. (no Refs)

VIRAL STUDIES IN HUMAN CANCER

60. EXPRESSION OF RETROVIRUSES TRANSFORMING GENES IN HUMAN SOLID TUMORS (MEETING ABSTRACT)

Eva A, Rubbins K, Anderson P, Srinivasan A, Papas T, Tronick S, Reddy EP, Westin E, Wong-Staal E, Ellmore N, Gallo R, Aaronson SA

National Cancer Institute, Bethesda, MD

10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

DNA fragments comprising the onc genes of molecularly cloned transforming retroviruses including SSV, BALB-MSV, Albelson MuLV, and MC29 were used as probes for detection of related transcripts in human cells. These four retroviruses are known to be capable of inducing a wide range of malignancies. Moreover, their onc genes, while unrelated to each other, possessed sufficient homology with human DNA so as to detect related information at low copy number with reasonably high single intensity. The human tumor cells used in these studies were malignant in athymic nude mice where they reproduced the histopathology of the original tumors. The approach utilized for detection of viral-related transcripts in human tumor cells involved poly(A)-selection and analysis by agarose gel electrophoresis and RNA blotting techniques. This analysis revealed the presence in all of the cell lines analyzed of multiple RNA species that hybridized to probes specific for the transforming genes of BALB-MSV and Abelson-MuLV. A single transcript was detected with the MC29 onc gene probe. In some tumors, the level of this transcript was elevated at least 5 to 10 fold over that present in normal cells or other tumor cell lines. Finally, the SSV onc probe detected a single transcript specifically in sarcoma and glioblastoma-derived tumor cell lines. (no Refs)

61. THE FIRST REAL HUMAN TYPE-C RETROVIRUS.

Epstein MA
Dept. Pathology, Univ. Bristol, Bristol BS8 ITD, England
Immunol Today; 3(3):61-62 1982

Recent advances with respect to the human T leukemia virus (HTLV) are reviewed. HTLV may eventually be proven the etiological agent in adult T cell leukemia, thus adding HTLV to the known association of Epstein-Barr virus with Burkitt's lymphoma and nasopharyngeal carcinoma and hepatitis B virus with primary hepatocellular carcinoma. Human oncogenic viruses may be responsible for a very significant proportion of human malignant disease worldwide. (7 Refs)

62. SEX PARTNERS AND HERPES SIMPLEX VIRUS TYPE 2 IN THE EPIDEMIOLOGY OF CANCER OF THE CERVIX.

Graham S, Rawls W, Swanson M, McCurtis J
Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, 2211 Main St., Buffalo, NY, 14214
Am J Epidemiol; 115(5):729-735 1982

The authors examined the interaction of exposure to various numbers of sex partners and evidence of antibodies to herpes simplex virus type 2 (HSV-2) in cervical neoplasia in 181 cases of cervical dysplasia, carcinoma in situ and cancer of the cervix and 130 control patients in Los Angeles County, California hospitals, in 1974-1979. Studies by the authors and other investigators have found that risk of cancer of the cervix was enhanced with numbers of sex partners, frequency and duration of using the vaginal douche, early age at first pregnancy, and antibodies to HSV-2 as measured by radioimmunoassay. In this study, it was found that for women with only one or no sex partner in their history, risk was elevated if evidence of antibodies to HSV-2 were present. The same was true for women with two or more sex partners. The risk associated with two or more sex partners was not higher than that for women with one sex partner among those positive for HSV-2, and among those negative for HSV-2. Thus, although this inquiry needs replication on larger numbers of women, whatever the other microorganisms of carcinogens patients were exposed to with multiple sex partners, there was no apparent effect beyond the fact the HSV-2 raises the risk of cancer of the cervix. This may strengthen credence in the hypothesis that HSV-2 is an etiologic factor in cervical cancer. (Author abstract) (12 Refs)

63. VIRUS ISOLATION AND IDENTIFICATION IN CERVICAL CANCER PATIENTS.

Xiang J, Feng JS, Huang PT, Chen WK, Wu JG, Liu HY
Virus Res. Inst., Hubei Medical Coll., Hubei, People's Republic of China
Chin Med J [Engl]; 95(2):151-152 1982

Preliminary results of the isolation and classification of herpes simplex virus (HSV) strains from cervical specimens of cervical cancer patients are reported. Cervical prophylactic surveys are presented. Specimens consisted of 20 biopsy specimens, 53 patient specimens, and 256 prophylactic survey specimens. Seven virus strains were isolated: one (Bio 12) from cervical cancer biopsy; two (CC 21, CC 26) from patient exfoliated cell specimens; and four (4289, 4277, 4272, 4518) from prophylactic survey specimens. All strains were cytopathic to rabbit kidney cells and fetal lung monolayer cultures. Four strains (CC21, CC26, 4289, 4272) were examined by electron microscopicy and showed typical HSV morphology. Two of the strains (Bio12, CC26) were contaminated and could not be typed. The remaining five HSV strains were typed as follows: one HSV-1 strain, three HSV-2 strains, and one intermediate type strain (biologically HSV-2, but serologically HSV-1). All the patients from the prophylactic survey who yielded the four strains had severe cervical inflammation and were monitored for malignancy developments. (6 Refs)

64. MANAGING GENITAL HERPESVIRUS INFECTION: THE STATE OF THE ART.

Curole DN
Louisiana State Univ. Sch. Medicine, New Orleans, LA
Consultant; 21(6):47-49,53 1981

Symptoms of primary herpesvirus genital infection; recurrent infection; culture, smear, and antibody titer; management options; infection during pregnancy; and oncogenic potential are reviewed. Herpesvirus exposure frequently leads to infection, and recurrence is possible for 3 yr or longer. Cervical and vulvar cancer appear to be serious risks for women with herpesvirus infections. (no Refs)

65. KAPOSI'S SARCOMA - AN EMERGING EPIDEMIC.

Mansell PW
Div. Cancer Prevention, M. D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 34(2):72-74 1982

The pathobiology of Kaposi's sarcoma and the recent outbreak of the disease (greater than 200 cases) that has occurred among young male homosexuals are described. Kaposi's sarcoma may be associated with the DNA virus cytomegalovirus. It is also associated with immunosuppression and is a frequent second primary among cancer patients. The recent outbreak appears to be spreading from New York City, where 55% of the cases have originated. The population at risk (24-40 yr old) falls in age between that typical of American and European patients (60-70 yr) and that of African patients (less than 20 yr). All patients thus far examined have had anti-hepatitis B antibody or hepatitis B surface antigen, as well as anticytomegalovirus antibody titers. Cytomegalovirus has been cultured from tumor tissue in several cases. All patients in the outbreak have so far been immunosuppressed. The immunological defect appears to be progressive and long-lasting. All patients have had a history of sexually transmitted diseases, some with multiple manifestations such as hepatitis, genital herpes, gonorrhea, and condyloma. Mortality has been exceptionally high, with death occurring in a high percentage of patients within 20 mo, subsequent to unsuccessful combination chemotherapy with doxorubicin, bleomycin, Velban, and dacarbazine. Possible etiologic factors contributing to this outbreak and to malignant transformation in general are discussed. (23 Refs)

66. PERSISTENT, GENERALIZED LYMPHADENOPATHY AMONG HOMOSEXUAL MALES.

Mildvan D, Mathur U, Enlow R, Gold J, Sears C, Wong B, Brown AE, Henry S, Safai B, Arlin Z, Moore A, Metroka C, William DC, Siegal F, Brown J, Wallace J, Sencer D, Friedman SM, Felman YM, Rothenberg R, Sikes RK, Owen W, Dritz JS, Rendon C, Chin J, Sonnabend J, Israel E
(c/o Israel), Public Health Service, Centers for Disease Control, Atlanta, GA, 30333
MMWR; 31(19):249-251 1982

Records are reviewed of 57 homosexual men with lymphadenopathy seen at various medical centers. There are many causes of generalized lymphadenopathy, including viral infections and cancer (including leukemia and lymphoma). The unexplained syndrome is of concern because of current reports of

Kaposi's sarcoma (KS) and opportunistic infections (OI) primarily in homosexual males. The epidemiological characteristics of the 57 reported cases are similar to those of the homosexual KS/OI. (6 Refs)

67. KAPOSI'S SARCOMA AND PNEUMOCYSTIS PNEUMONIA AMONG HOMOSEXUAL MEN - NEW YORK CITY AND CALIFORNIA.

Friedman-Klen A, Laubenstein L, Marmor M, Hymes K, Green J, Ragaz A, Gottleib J, Muggia F, Demopoulos R, Weintroub M, Williams D, Oliveri R, Marmer J, Wallace J, Halperin I, Gillooley JF, Prose N, Klein E, Vogel J, Safai B, Myskowski P, Urmacher C, Koziner B, Nisce L, Kris M, Armstrong D, Gold J, Mildran D
New York Medical Center, New York, NY
MMWR; 30(25):305-308 1981

Kaposi's sarcoma has been diagnosed in 26 homosexual men (26-51 yr old) during the past 30 mo in California and New York. All eight of the patients died within 24 mo after diagnosis. Serological evidence of past or present infection with cytomegalovirus was observed in 12/12 examined. This occurrence of Kaposi's sarcoma in so many young men in a period of only 30-mo was considered to be highly unusual. The fulminant clinical course reported in many of these patients also differed from that classically described for elderly persons. Physicians should be alert for Kaposi's sarcoma, Pneumocystis pneumonia, and other opportunistic infections associated with immunosuppression in homosexual men. (19 Refs)

68. LOSS OF IMMUNOCOMPETENCY IN HOMOSEXUALS: A NEW PROBLEM.

Hawkins JN, Smith JG
Dept. Dermatology, Medical Coll. Georgia, Augusta, GA, 30912
South Med J; 75(5):516-518 1982

Loss of immunocompetency and increased frequency of Kaposi's sarcoma (KS) in homosexuals is discussed. High serum antibody titers to cytomegalovirus (CMV) were present in all KS patients in whom it was tested. Homosexuals have long been known to have an increased incidence of many infections including hepatitis A and B, amebiasis, giardiasis, gonorrhea, syphilis, condylomata acuminata, and CMV. CMV is believed to be sexually transmitted, and this virus has been demonstrated in both urine and semen. CMV has been shown to cause immunosuppression in mice and human beings. Whether CMV is oncogenic is not known. (12 Refs)

69. OF WOODCHUCKS AND MEN: THE CONTINUING STORY OF HEPATITIS B AND HEPATOCELLULAR CARCINOMA.

Johnson PJ, Williams R
Liver Unit, King's Coll. Hosp. Medical Sch., London SE5 8RX, England
Br Med J; 284(6329):1586-1588 1982

Statistical evidence that presence of hepatitis B surface antigen (HBsAg) is associated with high rates of hepatocellular carcinoma is presented. Studies on the relationship between HBsAg and cirrhosis lead to the hypothesis that in susceptible people the hepatitis B virus causes either a healthy carrier state or chronic liver disease depending on the host's immunological reaction to the virus. After many years the virus becomes part of the host genetic material, and in some cases this may lead to malignant change. Potential uses of vaccines against hepatitis B virus or antiviral chemotherapy in carriers are discussed. (22 Refs)

70. EPIDEMIOLOGY, EARLY DIAGNOSIS AND TREATMENT OF LIVER CELL CANCER.

Tsung-Tang S, Zhao-You T, Yuan-Yun C
Cancer Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

Possible etiological factors, mechanism of carcinogenesis, early diagnosis, and surgical treatment of liver cell cancer are reviewed. Topics include epidemiology (geographic distributions, hepatotoxins, hepatitis B virus, host factors, prevention trials), early diagnosis (alpha fetoprotein serology, hepatoangiography, ultrasonography, computerized tomography, radionuclide imaging, tumor markers other than alpha fetoprotein), and treatment (early treatment of mass survey patients and ultimate outcome, surgical resection, surgical approach to nonresectable cases, conservative treatment of liver cell cancer). (147 Refs)

71. EVIDENCE THAT HEPATITIS B VIRUS HAS A ROLE IN LIVER-CELL CARCINOMA IN ALCOHOLIC LIVER DISEASE.

Brechot C, Nalpas B, Courouce AM, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P
Unite de Recombinaison et Expression Genetique, Institut Pasteur, 28 rue du Docteur Roux, 75015 Paris, France
N Engl J Med; 306(23):1384-1387 1982

Determinations of hepatitis B virus (HBV) DNA were made in a prospective study of 51 alcoholics without hepatocellular carcinoma (HCC) and in a retrospective study of 20 alcoholics with both alcoholic cirrhosis and HCC. The overall prevalence of HBV serologic markers was 37% in the first group, compared with 10% in a nonselected blood-donor population. HBV DNA was detected in liver samples from three hepatitis B surface antigen (HBsAg)-positive patients from the first group and in liver samples of five other patients from this group in whom serum HBsAg was not detectable. In the second group, HBV DNA was detected in the neoplastic portion of the autopsied liver in all patients. Integration of viral DNA into the hepatocellular DNA was demonstrated in the samples from the second group, but conclusively in only two samples from the first group. HBV DNA was not detected in the livers of 14/16 patients with alcoholic liver disease (from the first group) who were negative for HBsAg but positive for anti-hepatitis B core antigen or anti-HBsAG, suggesting that HBV is probably not involved in progression of the liver disease. The presence of HBV DNA in livers of alcoholic patients without HCC may delineate the population at high risk for development of this disease. (25 Refs)

72. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K
Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan
Nippon Rinsho; 40(2):468-477 1982

World epidemiological surveys and molecular biology research on the relationship between hepatitis B virus (HBV) and liver cancer are discussed, and cases of hepatitis and hepatic cirrhosis which transformed into hepatic cancer in Japanese patients are analyzed. Various epidemiological and molecular biology studies show a clear correlation between HBV and hepatic cell carcinoma. Patients with B-type hepatitis, cirrhosis, or hepatic cancer were significantly younger than those with non-B type hepatitis, cirrhosis, or hepatic cancer, respectively. Approx 70% of 110 cases of hepatic cancer were found to have positive laboratory findings related to HBV. The patients who had chronic liver disease and who were positive for hepatitis Bs (HBs) antigen were thought to be at high risk for developing hepatic cancer. No direct relationship was observed between alpha-fetoprotein (AFP) levels and serum HBs antigens, however, monitoring levels of AFP was thought to be an important method to help detect early stage liver cancer. (33 Refs) (In JPN)

73. HEPATITIS-B VIRUS INFECTION IN BLACK CHILDREN WITH HEPATOCELLULAR CARCINOMA.

Kew MC, Hodkinson J, Paterson AC, Song E
Dept. Medicine, Witwatersrand Univ. Medical Sch., Hospital Hill, Johannesburg 2001, South Africa
J Med Virol; 9(3):201-207 1982

Six unselected South African black children (2 female, 15 and 16 yr old; 4 male, 10-13 yr old) with hepatocellular carcinoma (HCC) were examined for hepatitis-B virus (HBV) infection. Characteristics of the tumors were similar to those in black adults. All of the patients were positive for hepatitis B surface (HBs) antigen and hepatitis B core antigen in the serum. Hepatitis Be antigen was present in four patients; sera from the two patients without e antigen (1 male, 1 female) were positive for e antibody. All of the sera were negative for HBs antigen. Taken in conjunction with the HBV status of black adults in South Africa, the findings suggest the possibility that nearly all black patients with HCC are or have been infected with HBV. If HBV is oncogenic, tumor formation may occur within 10 yr of the initial infection. (14 Refs)

74. HEPATOCELLULAR CARCINOMA IN AN URBANISED BLACK COMMUNITY. A CHANGING PATTERN.

Paterson AC, Isaacson C
Dept. Pathology, Baragwanath Hosp., Sch. Pathology South African Inst. Medical Res., Johannesburg 2000, South Africa
Virchows Arch [Pathol Anat]; 395(3):273-278 1982

Hepatocellular carcinoma has been extensively studied in Southern Africa, and particularly its relationship to hepatitis B virus infection. Most of this work involved rural black populations. In this study the impact of urbanization on this relationship is investigated. The material is derived from the laboratory records at Baragwanath Hospital which serves the Black urban community of Soweto. Cases autopsied during the periods 1956-1960 and 1976-1980 have been examined with regard to age, sex, underlying cirrhosis and presence of HBsAg in the non-tumor liver. In addition, all biopsies from 1955 to 1980 have been analyzed with respect to age and sex. There is evidence of a significant increase in overall av age and in the proportion of female cases, while the percentage of HBsAg positive cases has fallen. Possible causes for these findings are considered. (Author abstract) (34 Refs)

75. HEPATITIS B AND PREVENTION OF HEPATOCELLULAR CARCINOMA.

Blumberg BS
Inst. for Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Nouv Presse Med; 11(12):903-905 1982

The role of a hepatitis B virus (HBV) vaccine in the prevention of hepatocellular carcinoma (HCC) is discussed. Production of the HBV vaccine, the relationship between HBV and HCC, and viruses similar to HBV are considered. Geographic regions with a high incidence of HBV surface antigen coincide with areas of high HCC incidence. Infection with HBV is most common among patients presenting with HCC compared to appropriate controls. (no Refs) (In FRE)

76. CLINICO-PATHOLOGICAL ANALYSES OF HIGH RISK FACTORS WITH HEPATIC CELL CARCINOMA IN CHRONIC LIVER DISEASES (MEETING ABSTRACT)

Ohtoh K, Ohno H, Okuyama Y, Tsubaki K, Ohkubo H, Ishizuka H, Fujita S, Kaneda H, Honda T, Karasawa T, Shikata T
Nihon University School of Medicine, Tokyo, Japan
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Until now, we have had 68 cases of hepatic cell carcinoma (HCC) which were diagnosed histologically. Fifty-six of them were accompanied with liver cirrhosis (LC). Of these patients 74% had positive HBV (hepatitis B virus) and 85% had positive AFP (alpha-fetoprotein). Of the patients of HCC without LC, very small number had both positive HBV and AFP. So, there seem to be some risk factors with HCC in chronic liver diseases. Then, in order to clarify these, patients with various chronic liver diseases who had been observed for 3 to 8 years, analyzed clinico-pathologically. Nineteen out of 120 patients with chronic hepatitis (87 active type (CAH), 33 inactive type (CIH)) had positive AFP. The percentage of AFP positive patients with CAH (21.8%) was higher than that of ones with CIH (6.1%). Of 118 patients with LC 50 had positive HBV. In patients with LC, the percentage of AFP positive ones with positive HBV (63%) was higher than that of ones with negative HBV (29%). Sixteen patients with CH and 43 with LC were followed for many years. Thirteen out of these 43 LC cases had HCC. Of 16 cases with CH 8 had positive AFP, and all the patients with positive AFP had positive HBV. Patients who had postive AFP had a tendency to have positive HBV. The AFP values at the initial examination in all the patients were less than 200ng/ml. It seems to be important in the early diagnosis of HCC to follow up patients with chronic liver diseases and HBV and AFP. It is also considered that the presence of HBV is an important factor in the occurrence of HCC. (no Refs)

77. HEPATITIS B VIRUS INFECTION IN HEPATOCELLULR CARCINOMA AND OTHER MALIGNANCIES (MEETING ABSTRACT)

Lim KP, Singh R, Oon CJ
University Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316, Singapore
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Patients with advanced malignant diseases have depressed cell mediated immunity and are vulnerable to various viral and opportunistic infections. Similarly patients with primary hepatocellular carcinoma (PHC) are also known to have a depressed immunity. Seropositive Hepatitis B virus (HBV) infections are common (70-90%) in PHC patients in the Asian Pacific Region and this country. Could this presence of the HBV in such PHC patients be due to a newly acquired HBV infection from a depressed immunity of malignancy or to a pre-existing infection by the HBV virus? We investigated this question in a pilot study on 56 PHC patients and 47 patients with other malignancies. During the period between January to July 1980 the sera of these patients and a random normal control group matched for age and sex were examined. Hepatitis B surface antigen (HBsAg) and antibody to Hepatitis B core antigen (HBcAb) were determined using commercial radioimmunoassay kits. In this study the incidence of HBs antigenemia in PHC patients was found to be higher than in normal individuals or in the tumor control group. In the latter two groups, the incidence of antigenemia was similar. The incidence of HB core antibody was also higher in PHC patients than in normal controls but not significantly different from the other tumor controls. (no Refs)

78. HISTOLOGIC AND SEROLOGIC EVALUATION OF HEPATOCELLULAR CARCINOMA (HCC) IN KOREA (MEETING ABSTRACT)

Chung WK, Chung KW, Sun HS, Kim BS, Hoofnagle JH, Minuk GY, Gerber MA, Thung S, Popper H
Department of Medicine, Catholic Medical Center, Seoul, Korea
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Independent needle biospy specimens were obtained by laparoscopy from noninvolved liver and from tumor in 33 patients with HCC and from nontumorous liver in 12 patients in whom HCC developed 1-13 years later. Routine microscopy revealed in the surrounding liver ground-glass hepatocytes 10 times, dysplastic hepatocytes 22 times, adenomatous nodules 21 times. In toto, potential precursor lesions were found in 75% of cases in the cancer stage and in 58% before. Shikata orcein stains for HBsAg were positive in 33%. These observations were elaborated by immunoperoxidase study for HBsAg, HBcAg and alpha-fetoprotein. Chronic active hepatitis (CAH) was found only 4 times while the tumor was present, and 9 times before the tumor was found, suggesting common regression of CAH at the cancer stage. Serologically in 83% HBsAg was found and in all remaining cases anti-HBc, suggesting association with hepatitis B infection in all cases, of which 38% also had serum HBeAg but only 3% had DNA polymerase. HCC in Korea is almost always associated with HB infection, has the characteristic cytologic precursor lesions, but usually little activity of the hepatitic process in the cancer stage, while viral replication appears to persist sometimes. (no Refs)

79. BURKITT-TYPE LYMPHOMA IN FRANCE AMONG NON-HODGKIN MALIGNANT LYMPHOMAS IN CAUCASIAN CHILDREN.

Philip T, Lenoir GM, Bryon PA, Gerard-Marchant R, Souillet G, Philippe N, Freycon F, Brunat-Mentigny M
Paediatric Oncology Unit, Centre Leon-Berard, 28, rue Laennec, 69273 Lyon cedex [illegible], France
Br J Cancer; 45(5):670-678 1982

In a retrospective analysis of 87 cases of Caucasian childhood non-Hodgkin malignant lymphoma (NHML) from Lyon, France, all the cases were diffuse lymphomas, but 47 were diagnosed as monomorphic small non-cleaved NHML, pathologically indistinguishable from Burkitt's lymphoma (BL). BL could then be the most frequent childhood lymphoma in France. This homogeneous series allows better definition of the characteristics of BL within NHML. Age distribution is similar to that of endemic BL, with a sex ratio of 3.7/1. Abdominal masses are initially present in 68% of the cases, whereas jaw is involved in only 4%. The disease is characterized by its overwhelming evolution in the absence of therapy. However, complete remission (CR) is usually obtained after the first chemotherapy regimen. Most relapses occur at 3-8 mo. Death could be related to cerebrospinal fluid (CSF) involvement, local recurrence or secondary marrow involvement. Ninety percent of the patients alive with no evidence of disease (NED) 8 mo after CR can be considered as definitely cured. Our study on Caucasian children with NHML indicates that, from histological and clinical criteria, nearly half the cases are very similar to African BL. Even though EBV rarely associated with our cases, BL could be a worldwide lymphoma. (Author abstract) (41 Refs)

80. SOCIAL CLASS AND AGE AT DIAGNOSIS OF HODGKIN'S DISEASE: NEW EPIDEMIOLOGIC EVIDENCE FOR THE 'TWO-DISEASE HYPOTHESIS'.

Gutensohn NM
677 Huntington Ave., Boston, MA, 02115
Cancer Treat Rep; 66(4):689-695 1982

The bimodality in the age-incidence pattern of Hodgkin's disease (HD) suggests that the disease may result from two causal pathways with differing age peaks. Among young adults, HD may develop as a rare consequence of a common infection (probably viral), with risk increasing with age at time of infection. However, among older persons, HD may result from other causes, probably similar to those of the other lymphomas. We evaluated this hypothesis in a population-based, case-control study in eastern Massachusetts involving 326 newly diagnosed cases (patients greater than or equal to 15 years of age) and 650 population controls. These subjects were compared for factors in childhood environment that influence age of exposure to common viruses, including subship size, parental education, and type of housing. Among young adult (15-39 years of age), risk of HD was associated with small family size, single-family housing, and relatively high maternal education, consistent with the delayed infectious exposure hypothesis. Among middle-aged persons (40-54 years of age), a similar pattern of social class risk factors was present. However, among older persons (greater than 55 years of age), risk was not associated with social class; if anything, patients were of somewhat lower social class background than controls. These findings are consistent with the 'two-disease hypothesis,' in that social class risk factors differed between younger and older persons. These findings, coupled with other epidemiologic observations, suggest that the pathogenesis of HD among older persons is independent of that among younger persons. (Author abstract) (10 Refs)

81. DIVERSITY AND PATHOLOGY OF THE LYMPHOCYTE.

Govaerts A
Faculte de Medecine, Universite Libre Bruxelles, Brussels, Belgium
Rev Med Brux; 3(4):235-236 1982

Lymphocytes have multiple and diverse functional properties. B lymphocytes have receptors for Epstein-Barr virus. Acute lymphoblastic leukemia corresponds to clonal development of T, B, or null cells. The viral etiology of certain human cancers has been singularly reinforced by the discovery of a retrovirus C in the cells of T lymphoid leukemias. The associations of the Epstein-Barr virus with Burkitt's syndrome and of hepatitis B virus with hepatic cancer, together with the discovery of human T leukemia virus, may lead to new studies that will permit a greater understanding of cancer immunotherapy. (no Refs) (In FRE)

82. IN VIVO CONTROL OF THE PROLIFERATIVE CAPACITY OF EPSTEIN-BARR VIRUS INFECTED B CELLS (MEETING ABSTRACT)

Klein E
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

The majority of individuals harbor EBV (Epstein-Barr) infected B cells (BEBV) and these are known to have a proliferative potential. Since proliferative accidents (tumor growth, chronic mononucleosis) are rare in vivo, these cells must be kept under rigorous control. The demonstration of cellular and serological recognition of BEBV cells indicates that immunology plays an important role. An interesting aspect of the host response is that the cells which can be infected by the virus (B lymphocytes) are a functional part of the immune system. Cell mediated immunological effector mechanism directed against BEBV cells include the natural killer phenomenon, activation of T cells by autologous B cells and the evolution of T cell memory to EBV antigens. It seems that the events in the infectious mononucleosis syndrome represent and amplified picture of the interaction between T and B lymphocytes in the immune response. Our in vitro studies of autologous systems permit comparison between and evaluation of several immunologic mechanisms that may operate in the cytotoxicity against or the growth inhibition of either freshly EBV-transformed or newly EBV-infected lymphocytes. The present findings suggest that antibody-dependent cellular cytotoxicity (ADCC) plays a basically important role in seropositive healthy individuals. This particular immunologic mechanism can be further enhanced by addition of even a small amount of interferon. EBV is widespread in man with antibody response and a small amount of interferon is possibly present normally. The cooperation of lymphocytes, EBV antibodies and interferon is therefore considered the most effective mechanism in the protection against EBV-induced oncogenesis in man. (no Refs)

83. CLUES TO PATHOGENESIS OF EPSTEIN-BARR VIRUS-INDUCED DISEASES FROM ANALYSIS OF 100 CASES OF X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP) (MEETING ABSTRACT)

Purtilo D, Sakamoto K, Barnabei V, Seeley J
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

Comprehensive analysis of 100 cases in the Registry of XLP revealed four major phenotypes Epstein-Barr virus (EBV) infection: 1) infectious mononucleosis (IM) including 42 fatal cases without coexisting phenotypes and 32 with other phenotypes; 2) all 18 cases of aplastic anemia occurred with IM or malignant lymphoma (ML) and never did aplastic anemia occur simultaneously with agammaglobulinemia; 3) 32 cases of ML (B cell types only) including 16 cases solely and 16 with IM; and 4) agammaglobulinemia affected 16 boys, usually with IM or ML. Rarely, 3 phenotypes occurred simultaneously. Long-term anti-viral capsid antigen (VCA), -early antigen (EA), and -EB nuclear antigen (EBNA) antibody studies of families with XLP showed geometric mean (GMT, reciprocal) titers on 11 XLP patients and 11 mothers are summarized. Males have profound T and B cell and natural killer cell immune defects to EBV. Several carrier females exhibit IgA and IgM anti-VCA and anti-EA indicating persistent infection due to their partial immunodeficiency of XLP. Our molecular hybridization studies of tissues of seven XLP patients reveal EBV genome in all cases. (no Refs)

84. CHARACTERIZATION OF PRE-NASOPHARYNGEAL CARCINOMA CONDITIONS IN CHINESE (MEETING ABSTRACT)

de The G, Zeng Y, Desgranges C
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

The presence of antibody in the IgA class against the structural antigens of the EBV as well as the early antigens is a very discriminatory tool for the diagnosis of nasopharyngeal carcinoma (NPC). These markers are also very instrumental to carry out mass surveys for early detection of these tumors in endemic areas. The mass serological and clinical surveys carried out in the Guang-Xi Autonomous Region by Zeng et al provided a situation where we were able to investigate the presence of viral markers in the mucosa of IgA positive but clinically normal individuals. Out of 67 such individuals who were found IgA/VCA (viral capsid antigen) positive in 1979, 56 were found to remain positive in 1980 and to exhibit some abnormalities in their nasopharyngeal mucosa. They were biopsied and their serum and saliva tested. Four NPC were detected and in 17 individuals with no detectable histopathological lesion, viral markers were found in the nasopharyngeal mucosa. Although we do not know yet the proportion of IgA negative individuals who might have viral markers in their mucosa, we would like to propose as a working hypothesis that pre-cancerous conditions exist for NPC and are related to the presence of IgA/VCA antibodies and of viral markers in the nasopharyngeal mucosa. (no Refs)

85. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML
Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536
Neurosurgery; 10(5):643-662 1982

The literature on viral induction of intracranial tumors is reviewed, with special emphasis on the papovaviruses of the simian virus (SV)40 group. Discussion includes oncogenic studies in vivo and in vitro, the molecular basis for infection and transformation, and evidence that the papovavirus may cause human intracranial tumors. The latter was partly obtained from studies on children inoculated with live polio virus contaminated with SV40 who developed an excess of tumors, including intracranial tumors. (188 Refs)

86. DIFFERENT PAPILLOMAVIRUSES AS THE CAUSES OF ORAL WARTS.

Lutzner M, Kuffer R, Blanchet-Bardon C, Croissant O
Unite des Papillomavirus, Institut Pasteur, 25 rue du Docteur Roux, 75724 Paris 15, France
Arch Dermatol; 118(6):393-399 1982

We have observed four patients with oral papillomas. Two children had oral mucosal lesions characteristic of focal epithelial hyperplasia, a young man had common, wart-like lesions on his hard palate, and a male immunosuppressed renal allograft recipient had condyloma-like lesions on his gingivae. Papillomavirus-like particles were seen by electron microscopy in lesions from both patients with focal epithelial hyperplasia. No structural antigens for human papillomavirus (HPV) 1, 2, 3, or 5 were found by immunofluorescent microscopy, but further evidence of the presence of a papillomavirus was found by immunoperoxidase microscopy using a cross-reacting sodium lauryl sulfate-disrupted bovine papillomavirus 1 anti-rabbit serum sample. The distinct histologic pattern seen in focal epithelial hyperplasia suggests that a yet undescribed HPV type might be associated with this disease. Histologic, ultrastructural, and immunofluorescent microscopy and restriction endonuclease analysis all gave evidence of HPV 2 in the palatal lesions in patient 3. Evidence of papillomavirus antigen was found by immunoperoxidase microscopy in the oral condylomas from our immunosuppressed patient. (Author abstract) (31 Refs)

87. CONCURRENT CARCINOMA OF PENIS AND CARCINOMA IN SITU OF THE CERVIX IN A MARRIED COUPLE. CASE REPORT.

Cocks PS, Adib RS, Hunt KM
Dept. Obstetrics and Gynaecology, Westmead Centre, Westmead NSW 2145, Australia
Br J Obstet Gynaecol; 89(5):408-409 1982

Carcinoma in situ of the cervix was detected in an 35-yr-old asymptomatic female as the result of a deliberate policy of taking cervical smears from partners of men with penile cancer. A 38-yr-old man had been referred to the hospital with a 5-mo history of a painful lesion on the glans penis that had recently bled after coitus. The patient's wife, para 5, had atypical cells with a suggestion of wart virus infection on a cervical smear requested as the result of her husband's penile lesion. A subsequent cervical smear has been reported negative for malignant cells. (6 Refs)

88. DERMATOLOGY.

Pearson RW
Dept. Dermatology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL
JAMA; 247(21):2946-2947 1982

Three areas of special interest among newly emerging trends in dermatology are reviewed. Newer synthetic retinoids have been successful in treating skin disorders; isotretinoin and etretinate have exhibited teratogenicity and induced several metabolic and other problems. Kaposi's syndrome has recently become epidemic in young homosexual males; immunodeficiency, possibly related to cytomegalovirus and Epstein-Barr virus, is an important factor. Recent results question the benign nature of lymphocytoma cutis and lymphomatoid papulosis. (13 Refs)

89. OBSTETRICS AND GYNECOLOGY.

Hill EC
Dept. Obstetrics, Gynecology, and Reproductive Sciences, Univ. California, San Francisco, CA
JAMA; 247(21):2966-2968 1982

Three important new developments in obstetrics and gynecology are reviewed. In vitro fertilization and embryo transfer was accomplished after the introduction of estrogen level control. Prenatal diagnosis and treatment has developed in recent years to include amniocentesis, ultrasonography, radiography, and fetoscopy; the procedures contribute to better management of pregnancy, labor and delivery, and care of the neonate. Early cervical neoplasia has been related to a number of viruses, including herpes simplex type 2, cytomegalovirus, and the papilloma virus. (13 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

90. A TRIAL OF TOPICAL ACYCLOVIR IN GENITAL HERPES SIMPLEX VIRUS INFECTIONS.

Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK
Virology Lab., Children's Orthopedic Hosp. Medical Center, P.O. Box C5371, Seattle, WA, 98105
N Engl J Med; 306(22):1313-1319 1982

Use of topically applied 5% acyclovir (AC) ointment for the treatment of first and recurrent episodes of genital herpes simplex virus (HSV) infections was evaluated in a multicenter double-blind placebo-controlled trial. Seventy-seven patients (25 men, 52 women; mean age 27 yr) with first episodes of HSV were treated. Of the 77 patients, 49 had primary genital herpes, while the other 28 had HSV neutralizing antibody detected in acute-phase serum and therefore had non-primary first episodes. Pretreatment viral titers, lesions areas, and lesion sizes were similar in control and AC-treated patients. The mean duration of viral shedding from external genital lesions was 0.95 days in the 53 AC-treated patients, as compared with 1.90 days in the 58 placebo-treated patients. In men, the mean time to crusting (2.7 days) and healing (6.9 days) of Group 1 lesions (lesions present at first visit) tended to be shorter in those given AC than in those given placebo (2.9 and 8.4 days, respectively). In women, the mean time to crusting and healing of both Group 1 and all external genital lesions were similar in the AC and placebo groups. In patients with recurrent genital HSV infection, new lesions developed during the course of therapy in 17/53 treated with AC and in 31/58 treated with placebo. The mean duration of local pain after start of therapy was 2.1 days in AC-treated men, as compared with 3.1 days in placebo-treated men. Among women, the mean duration was 2.7 days in those given acyclovir and 4.0 days in those given placebo. Medication was discontinued because of local pain in one patient who received the placebo. Transient irritation was reported in 11% of AC-treated patients. Incidence of recurrence was studied for AC-treated and control patients. (19 Refs)

91. ALTERED THYMIDINE KINASE IN SOME HUMAN LEUKEMIAS AS A POTENTIAL TARGET FOR SELECTIVE CHEMOTHERAPY (MEETING ABSTRACT)

Srivastava S
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

The selective antiherpes action of 1-beta-D arabinofuranosyl thymine (ara-T) derives from its susceptibility to phosphorylation by herpes simplex virus (HSV) specific thymidine kinase but not by cellular thymidine kinase. We now report that ara-T has been found to be cytotoxic (ID50 equals 8 uM) to two pre-B (one Philadelphia chromosome positive), and several T-human leukemic cell lines but not to one non-T/non-B, two myeloid and one B-cell line or to phytohemagglutinin stimulated normal human lymphocytes. All cell lines examined had comparable thymidine kinase activity, were free of HSV and were not inhibited by 5-propyl deoxyuridine or by acyclovir which are also phosphorylated by HSV specific thymidine kinase. The cytotoxic effect of ara-T was reversed by thymidine deoxyuridine but not by uridine. An ara-C (cytosine arabinoside) resistant cell line which lacked deoxycytidine kinase but not thymidine kinase activity was sensitive to ara-T. In contrast ara-T was inactive against two thymidine resistant T-cell lines which lacked thymidine kinase. (no Refs)

92. SENSITIVITY AND RESISTANCE OF HUMAN TUMOUR CELLS TO INTERFERON AND RINRCN.

Lin SL, Greene JJ, Ts'o PO, Carter WA
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Nature; 297(5865):417-419 1982

The antiproliferative effects of interferon (IFN) and double stranded (ds)RNA on human HT1080 fibrosarcoma and RT4 epidermal carcinoma cell lines were characterized using Luria-Delbruck fluctuation analysis of IFN resistance (IFNr). Examination of isolated colonies derived from resistant populations revealed that IFNr cells possess the same population doubling times in the presence and absence of IFN at concentrations normally resulting in complete cessation of growth. Consistent with the idea that IFNr is an induced trait, resistant colonies reverted to a sensitive state after varying lengths of time. In the resistant state, cells were at least as sensitive as their parental populations to the antiviral effects of IFN when vesicular stomatitis virus was used as the challenge virus, suggesting that resistance to the antiproliferative effects of IFN does not necessarily correlate with changes in sensitivity to its antiviral effects. The sensitivities of the IFNr lines to the antiproliferative effects of the synthetic dsRNA, rInrCn, were characterized. Resistant lines of both HT1080-2 and RT4-1 clones displayed the same sensitivity to rInrCn-mediated toxicity as did their respective parental HT1080-2 and RT4-1 lines. Luria-Delbruck analysis indicated that the INFr trait is a non-randomly acquired phenotype probably induced by IFN at the time of selection. The IFNr cells retain sensitivity to the antiviral effects of IFN, as well as to the antiproliferative effects of dsRNA. (24 Refs)

93. INTERFERON THERAPY.

World Health Organization Scientific Group on Interferon Therapy
World Health Organization, Geneva, Switzerland
WHO Tech Rep Ser (676): 28 pp., 1982.

Recent advances in interferon (IFN) production and clinical effects are reviewed. Production of human IFN (human interferon alpha, human interferon-beta, human interferon-gamma) with WBC and viruses, B-lymphoblastoid cells and virus, fibroblasts and double-stranded RNA, or a combination of WBC or T-lymphoblastoid cells with mitogen is described. Use of bacteria and yeast for producing IFN by recombinant techniques is relatively low in cost. Origin of human blood cells and cultured human cells used for IFN production, production and purification processes, and the possibility of longe-term consequences of IFN therapy must be carefully monitored. Standardization and measurement of biological activity is discussed. IFN have been beneficial in treating herpetic keratitis, herpes zoster, and laryngeal papilloma. IFN in combination with antiviral drugs may be useful for patients with chronic hepatitis B infections. In malignant disease, complete tumor regression has rarely been reported with IFN, although objective improvements have been seen in cases with multiple myeloma, disseminated follicular lymphoma, and recurrent breast cancer with systemic IFN. Occasional responses have been reported with other tumors. Use of IFN for treetment of malignant disease in man remains experimental and its clinical benefit is not proven. The max tolerated dose and the biologically effective dose must be defined for different tumors. (26 Refs)

94. SYNTHESIS OF PREMATURELY TERMINATED LATE TRANSCRIPTS OF POLYOMA VIRUS DNA IS RESISTANT TO INHIBITION BY 5,6-DICHLORO-1-BETA-D-RIBOFURANOSYLBENZIMIDAZOLE.

Montandon PE, Acheson NH
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Gen Virol; 59(part2):367-376 1982

Exposure of mouse kidney cells to 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB) (75 to 300 uM) during the late phase of infection by polyoma virus resulted in nearly complete (90 to 98%) inhibition of virus RNA synthesis. Sedimentation analysis revealed that, although the synthesis of high mol wt (greater than 10S) virus RNA was inhibited in a manner parallel to that of total virus RNA, the synthesis of small (3S to 7S) virus RNA was inhibited by only 40 to 50% in the presence of DRB. As a result, virus RNA synthesized in the presence of DRB contained a peak at 3S to 7S in addition to residual high mol wt virus RNA. Small virus RNA from either untreated or DRB-treated cells contained three- to six-fold higher levels of transcripts from the DNA fragment which lies between the BamHI and BglI sites (58.0 to 72.2 map units) than from DNA fragments covering the rest of the virus genome. Furthermore, 80% of the small RNA which hybridized to this fragment was complementary to the L strand of virus DNA. These results suggest that L strand transcripts are initiated within the BglI-BamHI DNA fragment and that a portion of these transcripts is prematurely terminated within several hundred nucleotides of the site(s) of initiation. DRB had little effect on the synthesis of these prematurely terminated RNAs. (Author abstract) (33 Refs)

95. MECHANISM OF ACTION OF DICHLORO-BETA-D-RIBOFURANOSYLBENZIMIDAZOLE: EFFECT ON IN VITRO TRANSCRIPTION.

Zandomeni R, Mittleman B, Bunick D, Ackerman S, Weinmann R
Wistar Inst. Anatomy and Biology, 36th and Spruce St., Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 79(10,part1):3167-3170 1982

The adenosine analog 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB) and its mono- and triphosphate derivatives inhibit RNA polymerase II-specific transcription in an extract of whole HeLa cells. The analog does not inhibit RNA polymerase III-specific adenovirus VA RNA transcription in the whole cell extract. With purified RNA polymerase II under nonspecific transcription conditions, no effect of DRB could be detected. DRB is equally effective in inhibiting in vitro transcription from several of the adenovirus promoters and the human epsilon-globin gene. The inhibitory effects are in the order DRB greater than DRB monophosphate greater than DRB triphosphate. Thus DRB acts in vitro presumably on systems in which specific RNA polymerase II initiation of transcription occurs and with no detectable effect on premature termination. This will provide a suitable model for study of the molecular mechanism of action of DRB on transcription. (Author abstract) (24 Refs)

96. POLYMERIC DERIVATIVES BASED ON CIS-DIAMMINEDICHLOROPLATINUM(II) AS ANTINEOPLASTIC AGENTS.

Carraher CE, Scott WJ, Lopez I, Cerutis DR, Manek T
Dept. Chemistry, Wright State Univ., Dayton, OH, 45435
ACS Symp Ser; 186:221-231 1982

The synthesis and physical characterization and biological testing of platinum polyamines (PP) are reviewed. The polyamines are readily synthesized through reaction of divalent PtX(4) salts with diamines. The polyamines show good antineoplastic activity against a wide range of tumors. Twelve PP were tested against mouse connective tissue tumor cells (L929 and L), human amnion transformed (WISH) cells, human cervical (HeLa) cells, and African Green Monkey Kidney transformed cells (VERD). The max (threshold) nontoxic level was similar for all compounds tested against tumor and transformed lines, being about 1-20 ug/ml; all were cytopathic above 30 ug/ml. In studies with selected polyamines, varied results were obtained against certain viruses. For poliovirus, PP can effect an increase or decrease in growth of virus or exhibit no effect at concentrations below those that affect HeLa cells. Similar results were found for PP in L929 cells infected with encephalomyocarditis virus (strain MM). A preliminary study showed that mice can tolerate a dose of 400 ug of one of the compounds; this dose is 10x greater than that needed to destroy either HeLa or L929 tumor cells. (28 Refs)

GENERAL REVIEWS

97. CANCER: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS FOR THE 1980S. VOLUME 1.

Burchenal JH, Oettgen HF
Memorial Sloan-Kettering Cancer Center, New York, NY
Cancer: Achievements, Challenges, and Prospects for the 1980s. Volume 1. New York, Grune and Stratton, 685 pp., 1981.

The current status of cancer research and prospects for the future are reviewed. Topics include epidemiology (analytic epidemiology, epidemiology and cancer control policy), viruses (polyoma, feline leukemia, sarcoma, Epstein-Barr viruses, retroviruses), radiation hazards (radiation and thyroid, breast, and childhood cancers), industrial and lifestyle carcinogens (metabolic activation of chemical carcinogens, tumor registries), host defense against cancer (immunogenetics of cancer in man and animals, cell-mediated immune reactions to human cancer antigens and their regulation, biochemistry of human tumor antigens), genetics (genetic epidemiology of human cancer, specific fine structural chromosome defects in human neoplasia, clinical features and management of genetic cancers), cell biology and cancer (evolution of the malignant cell phenotype, properties of metastatic tumor cells), prevention of carcinogenesis (inhibitors of chemical carcinogens, advances in the use of retinoids for cancer prevention, blocking of tumor promotion by protease inhibitors), and advances in diagnosis (biochemical and immunologic diagnosis of cancer, advances in nuclear imaging, early diagnosis of liver cancer, advances in diagnosis of gastrointestinal neoplasms). (1641 Refs)

98. VIRAL HEPATITIS. 1981 INTERNATIONAL SYMPOSIUM.

Szmuness W, Alter HJ, Maynard JE
Lab. Epidemiology, Lindsley F. Kimball Res. Inst., New York Blood Center, New York, NY
Viral Hepatitis. 1981 International Symposium. Philadelphia, The Franklin Institute Press, 843 pp., 1982.

Previously unpublished reports concerning viral hepatitis were presented and discussed. Topics ranged from molecular biology to vaccine development, from hepatitis virus culture to the treatment of clinical disease, from hepatoma in the woodchuck to the association of hepatitis B virus (HBV) infection with hepatocellular carcinoma in man. New insights into the molecular anatomy of hepatitis A and B viruses were presented and the in vitro propagation of whole virus or virus-related proteins was described. DNA viruses termed 'hepadna' include human HBV and related viruses found in the woodchuck, ground squirrel, and Pekin duck. The high occurrence of hepatocellular carcinoma among animals infected with HBV-like viruses provided strong virologic support for the epidemiologic data that suggests a causal relationship between HBV infection and the development of human hepatocellular carcinoma. The epidemiology, diagnosis, pathogenesis, and chronic sequelae of hepatitis B and the evolving clinical spectrum of non-A, non-B hepatitis were discussed. Passive and active immunization programs in Australia, Japan, England, Holland, Senegal, and the United States were reported. Overall, the subunit vaccine was safe, highly immunogenic, and almost completely protective among persons who responded with development of anti-surface antibody. Abstracts and summaries of 14 workshops are presented. Unresolved issues included measures to prevent intrahospital transmission of HBV, reduction of posttransfusion hepatitis, use of corticosteroids for treatment of chronic hepatitis, and the use of hepatitis B immunoglobulin in the prevention of type B hepatitis. (1302 Refs)

OTHER RELATED STUDIES

99. HUMAN LYMPHOMA-LYMPHOMA HYBRIDS AND LYMPHOMA-LEUKEMIA HYBRIDS. II. EPSTEIN-BARR VIRUS INDUCTION PATTERNS.

Klein G, Zeuthen J, Ber R, Ernberg I
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
JNCI; 68(2):197-202 1982

In addition to the spontaneous expression of markers of the early and late phases of the viral cycle [Epstein-Barr virus (EBV), early viral cycle antigens (EA), and viral capsid antigen (VCA)] by a panel of hybrid cell lines derived by fusion of human hematopoietic cell lines, the induction of these markers by three chemical inducers [5-iodo-2'-deoxyuridine, the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA), and sodium butyrate] were analyzed. A variant of the prototype producer of lytic EBV, P3HR-1 (PICAT) was observed to show consistent low spontaneous and induced production of EA and VCA as compared to the P3HR-1 line from which it was derived. An 'autohybrid' (PICATPO-1) between these two lines showed a low production of VCA. Hybrids between Raji and P3HR-1 sublines (RUD-PICAT-1 and RUDPUT-2) showed reduced expression of EBV antigens. Both hybrids were capable of VCA expression, in contrast to the Raji parent that expressed EA but not VCA. A new Raji-Daudi hybrid

(DITRUD-1) expressed spontaneous and induced EA and VCA at levels intermediate between its two parents. A different type of hybrid was derived from a Daudi subline and the K562 leukemia cell line (DUTKO-1) and was found to be capable of spontaneous as well as induced EA and VCA expression. Both DUTKO-1 and DITRUD-1 were similar to Daudi in their induction profile in respect to a very low response to TPA. (Author abstract) (20 Refs)

100. HUMAN LYMPHOMA-LYMPHOMA HYBRIDS AND LYMPHOMA-LEUKEMIA HYBRIDS. I. ISOLATION, CHARACTERIZATION, CELL SURFACE MARKERS, AND B-CELL MARKERS.

Zeuthen J, Klein G, Ber R, Masucci G, Bisballe S, Povey S, Terasaki P, Ralph P
Inst. Human Genetics, Univ. Aarhus, The Bartholin Building, DK-8000 Aarhus C, Denmark
JNCI; 68(2):179-195 1982

Four new somatic cell hybrids were obtained by fusion of various Burkitt's lymphoma (BL)-derived cell lines that had different selective markers: Raji-P3HR-1, Daudi-Raji, and a P3HR-1-P3HR-1 'autohybrid' derived from two P3HR-1 sublines. In addition, a hybrid was was obtained between the Daudi (BL) line and the human leukemia cell line K562. The hybrids were extensively characterized by means of chromosome, isozyme, and HLA surface markers. The phenotypic differences between the parent cell lines allowed some conclusions with respect to the expression of latent Epstein-Barr virus (EBV) genomes, C3 and EBV receptors, and of immunoglobulin and beta 2-microglobulin-HLA expression as well as the influence of the leukemia cell (K562) genome on B-cell properties in the Daudi-K562 hybrid. B-cell and differentiated markers of these hybrids were characterized. High-level expression dominated for the markers C3 and EBV receptors, which showed a good correlation coefficient of 0.84, as was true for Fc receptors and surface immunoglobulin. The Daudi-K562 hybrid showed loss of all B-cell markers but retention of the leukemia cell markers (eg, hemoglobin synthesis). (Author abstract) (59 Refs)

101. DISTRIBUTION OF INTERCELLULAR, INTRACYTOPLASMIC AND SURFACE IMMUNOGLOBULINS IN TYPE B NON-HODGKIN'S LYMPHOMA: EMPLOYMENT OF INDIRECT IMMUNOFLUORESCENCE IN THE DETECTION OF IMMUNOMORPHOLOGICAL FEATURES.

Pansa E, Risio M, Bernardi A, Griselli B, Funaro A
Lab. Histopathology, Oncology Dept., Ospedale Maggiore di San Giovanni Battista, Torino, Italy
Pathologica; 74(1029):33-45 1982

Immunomorphological patterns of the distribution of surface (SIg) and intracytoplasmic (CIg) immunoglobulins and free intercellular immunoglobulins (Ig) were examined by immunofluorescence (IF) techniques in 43 patients with type B non-Hodgkin's lymphomas and in 19 patients with reactive hyperplasias. In reactive hyperplasia, primary follicles displayed only SIg-positive cells arranged in a 'honeycomb' pattern; secondary follicles were observed in three concentric areas. In lymphocytic lymphoma (4 cases), the honeycomb pattern was usually observed; the pattern was evenly distributed on the node surface. Very few cells displayed cytoplasmic positivity. Immunocytomas (5 cases) showed diffuse, variously intense SIg-positivity; numerous CIg-positive cells were scattered throughout the preparation. Diffuse centrocytic, centroblastic/centrocytic, and centroblastic lymphomas displayed alternate honeycomb and reticulum areas, interspersed with completely negative areas. Few CIg-positive cells were observed. Monoclonality was seen in two cases. Follicular forms observed in 16 cases of centroblastic/centrocytic lymphoma were usually IF-negative. Very weak honeycombs were detected. Some av size CIg-positive cells were noted in six cases. Completely negative areas interspersed with fields of limited size that displayed weak reticulum or honeycomb positivity in lymphoblastic lymphomas (4 cases). CIg-positive cells were uniformly distributed with monoclonality in two cases. Characteristics of immunoblastic lymphoma (2 cases) were attributable to CIg-positive cells. Probable monoclonality was observed in two cases. (26 Refs)

102. REACTIVATION OF EPSTEIN-BARR VIRUS IN PREGNANT WOMEN: SOCIAL FACTORS, AND IMMUNE COMPETENCE AS DETERMINANTS OF LYMPHOPROLIFERATIVE DISEASES - A HYPOTHESIS.

Purtilo DT, Sakamoto K

Dept. Pathology, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105

Med Hypotheses; 8(4):401-408 1982

Epstein-Barr virus (EBV) appears to be reactivated in women during pregnancy, with resulting formation of anti-EBV antibodies. The stage in life at which an individual is infected by EBV appears to have an effect on the results of infection. Early infection, as might occur when a young child is exposed to his pregnant mother, may result in silent seroconversion. If exposure does not happen until later in life the result may be infectious mononucleosis. Thus, the time of infection may be related to the number of children in a family which sometimes is related to social class. (29 Refs)

103. FUSION OF EBV TRANSFORMED B CELL LINES WITH MURINE MYELOMAS AS A VIABLE ALTERNATIVE FOR PRODUCTION OF HUMAN MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Kozbor D, Chang TH, Steplewski Z, Roder JC, Koprowski H

Department of Microbiology and Immunology, Queen's University, Kingston, Canada

Hybridoma; 1(2):200 1982

Peripheral blood B lymphocytes from donors immunized with tetanus toxoid (TT) were preselected for antigen (TT) binding cells followed by transformation with Epstein Barr virus (EBV) and cloning. A clone (B6) secreting the highest amount of monoclonal anti-TT was fused with a non-Ig secreting murine myeloma (P3x63Ag8 variant 653), selected in HAT medium containing 10-5M Oubain and cloned. Four clones selected for study were found to secrete 10-fold more monoclonal anti-TT antibody (1-2 ug/ml IgM kappa) during the six day culture period, than the parental line (B6). Human x mouse hybridoma clones required much less serum (1%) for growth and Ig production. Hybrids have been stable for 5 months and possess a full complement of murine chromosomes and a mean of 24 human chromosomes. The results show that hybridomas between EBV lines and murine myelomas offer advantages of (1) increased stablity; (2) increased antibody production; and (3) reduced serum requirement for growth in vitro. Since EBV is a known polyclonal activator, this technique suggests the possibility of expanding human B cells of rare antigen specificities prior to fusion. (1 Ref)

104. ACUTE URINARY RETENTION AND TRANSIENT MOTOR PARALYTIC BLADDER ASSOCIATED WITH HERPES SIMPLEX GENITALIS.

Nielsen JB
Dept. Urology K, Aarhus Municipal Hosp., DK-8000 Aarhus C, Denmark
Urol Int; 37(1):57-60 1982

A case of transient urinary retention secondary to genital herpes simplex virus infection is reported. The neuropathy of the bladder was documented by a full urodynamic investigation including a positive denervation supersensitivity test. Viral infection as an etiology of transient bladder dysfunction is discussed. (Author abstract) (15 Refs)

105. HERPES ZOSTER AND VARICELLA IN CHILDREN WITH HODGKIN'S DISEASE.

Skovby F, Sullivan MP
Dept. Human Genetics, Yale Univ. Sch. Medicine, P.O. Box 3333, 333 Cedar St., New Haven, CT, 06510
Acta Paediatr Scand; 71(2):269-273 1982

Thirty-nine episodes of herpes zoster and varicella in 94 children with Hodgkin's disease were studied to determine the incidence and complications of these infections and their effect on the prognosis of Hodgkin's disease in children under multimodal treatment. Twenty-nine children (31%) developed herpes zoster and 7 (7%) had varicella. Three children had herpes zoster on two occasions. All children with varicella had uncomplicated infections. One patient died and three had visceral complications secondary to herpes zoster infections. Disseminated herpes zoster in nine children (10%) was more often associated with recurrent or active Hodgkin's disease and led to more complications than localized herpes zoster. Although varicella-zoster infection does not impair the prognosis of Hodgkin's disease, it is a potentially fatal infection and an affected child deserves vigorous treatment and support. (Author abstract) (19 Refs)

106. VARICELLA-ZOSTER-IMMUNOGLOBULIN AS A SAFE PROPHYLAXIS OF VARICELLA.

Kornhuber B, Kropp H, Ribeiro-Ayeh J, Hinderfeld L, Welte K
Zentrum der Kinderheilkunde, Abteilung fur Padiatrische Hamatologie und, Onkologie Klinikum der Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, D-6000 Frankfurt/Main 70, W. Germany
Monatsschr Kinderheilkd; 130(1):27-29 1982

Varicella immunoglobulin was administered on 298 occasions to children undergoing chemotherapy of malignant diseases after exposure to varicella. No serious side effects were observed. Varicella infections developed in four children; three of these infections were mild. No disabling varicella infections developed in any of the children. The immunoglobulin tested was more effective than other currently available methods of prophylaxis. (16 Refs) (In GER)

107. INCREASED EXPRESSION OF SV40 T ANTIGEN AND CELL DIVISION IN SKIN FIBROBLAST CELL LINES DERIVED FROM A FAMILY AT HIGH RISK OF CARCINOMA (FAMILY G OF WARTHIN).

Lubiniecki AS, Lynch HT, Blattner WA, Guirgis H
Flow Lab., Inc., Old Springhouse Road, McLean, VA, 22102
J Cancer Res Clin Oncol; 103(2):127-133 1982

T-antigen expression in 24 of 31 skin fibroblast cell lines from members of Family G was found to be significantly elevated compared with a healthy control population. However, the pattern of elevation did not appear to be associated with cancer risk. In addition, T-antigen values were independent of the age and sex, as well as the branch of family and generation of the cell donor. Cell lines from Family G tended to divide more frequently than cell lines from control donors. This tendency was negatively associated with elevated T-antigen expression in Family-G cell lines, while control cell lines showed no such correlation. These results demonstrate that caution must be taken in evaluating potential markers of cancer risk. Superficial analysis of the data would indicate the utility of the T-antigen assay as a marker for cancer family syndrome. However, consideration of additional factors, including pedigree relationships and cell biology in vitro, indicate that SV40 T-antigen expression is an ambiguous marker of this type of cancer risk, even when large groups are studied. (Author abstract) (14 Refs)

108. HUMAN PAPILLOMA VIRAL DNA REPLICATES AS A STABLE EPISOME IN CULTURED EPIDERMAL KERATINOCYTES.

LaPorta RF, Taichman LB
Dept. Oral Biology and Pathology, Sch. Dental Medicine, Health Sciences Center, State Univ. New York, Stony Brook, NY, 11794
Proc Natl Acad Sci USA; 79(11):3393-3397 1982

Human papilloma virus (HPV) is poorly understood because systems for its growth in tissue culture have not been developed. We report here that cultured human epidermal keratinocytes could be infected with HPV from plantar warts and that the viral DNA persisted and replicated as a stable episome. There were 50-200 copies of viral DNA per cell and there was no evidence to indicate integration of viral DNA into the cellular genome. There was also no evidence to suggest that viral DNA underwent productive replication. We conclude that cultured human epidermal keratinocytes may be a model for the study of certain aspects of HPV biology. (Author abstract) (27 Refs)

109. SYNTHESIS OF (2'-5')OLIGOADENYLATE AND ACTIVATION OF AN ENDORIBONUCLEASE IN INTERFERON-TREATED HELA CELLS INFECTED WITH REOVIRUS.

Nilsen TW, Maroney PA, Baglioni C
(c/o Baglioni) Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
J Virol; 42(3):1039-1045 1982

Treatment with interferon protected HeLa cells from infection with reovirus. This virus apparently activated an antiviral mechanism that was detected by the presence of (2'-5')oligoadenylate [(2'-5')An] in intact cells. The (2'-5')An was previously shown to activate an endoribonuclease, RNase L. We measured (2'-5')An by a sensitive competition-binding assay in cells infected at different multiplicities and for different lengths of time. Nanomolar concentrations of (2'-5')An were detected in cells infected at a multiplicity of greater than 5 after 2 hr of infection, the time at which the infecting virions were uncoated. The level of (2'-5')An increased up to 6 hr postinfection but declined afterward. To establish whether viral mRNAs were cleaved by RNase L, we analyzed the RNA extracted from infected cells by a highly specific hybridization assay on Northern blots. Full-sized reovirus mRNAs were detected in control infected cells, but not in interferon-treated infected cells, at 6 hr postinfection. At this time, a nuclease activity could be detected in these cells by demonstration of cleavage of rRNA, degradation of cellular mRNA, and polysome breakdown in the presence of emetine. Since this inhibitor freezes ribosomes, cleavage of mRNA between ribosomes could only be accounted for by an endonuclease, presumably RNase L. (Author abstract) (24 Refs)

110. CLINICAL ROLE OF THE STATE OF GRANULOCYTIC CHALONES IN JAUNDICE OF DIFFERENT ETIOLOGY.

Frolov VM, Rychnev VE
Dept. Infectious Diseases, N. N. Burdenko Medical Inst., Voronezh, USSR
Klin Med (Mosk): 60(3):76-82 1982

Diagnostic efficacy of serum leukopoietic activity (SLA) determination was studied in 310 patients with viral hepatitis, 46 with cancer of the head of the pancreas, 44 with cholecystitis, and 20 with Gilbert's disease. The patients with jaundice of tumoral etiology showed progressive increase of SLA, while the patients with jaundice due to a viral hepatitis showed marked decrease of SLA. (17 Refs) (In RUS)

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NOVEMBER, 1982

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. HERPESVIRUS SAIMIRI STRAIN VARIABILITY.

Desrosiers RC, Falk LA
Harvard Medical Sch., New England Regional Primate Res. Center, Southborough, MA, 01772
J Virol; 43(1):352-356 1982

Herpesvirus saimiri was isolated from 22 squirrel monkeys by cocultivation of peripheral lymphocytes with permissive owl monkey kidney monolayer cells. Comparison of virion DNA fragments produced from restriction endonuclease digestion was used as a sensitive measure of strain variability. Although all isolates contained similarities and common features, 19 of 22 were readily distinguished. Three of the isolates, however, were indistinguishable and possibly were related epidemiologically. Distinct subtypes of H saimiri were not evident by these criteria; Peruvian, Colombian, Guyanan, and Bolivian squirrel monkeys yielded isolates with characteristic features peculiar to the geographic region. Three of three colony-born squirrel monkeys that were tested yielded a strain of virus distinct from that obtained from the mother. In separate experi-

HE20.3173/2:

ments, two of three animals chosen at random yielded a strain of virus different from that originally obtained 16 and 22 months previously; only one of the three animals examined yielded the same strain of virus 22 months after the original isolation. The degree of restriction endonuclease fragment variability among H saimiri strains appeared to be greater than previously observed for other herpesviruses. (Author abstract) (23 Refs)

2. PURIFICATION OF POLYOMA VIRUS MEDIUM-SIZE TUMOR ANTIGEN BY IMMUNOAFFINITY CHROMATOGRAPHY.

Walter G, Hutchinson MA, Hunter T, Eckhart W
Institut fur Immunbiologie der Albert-Ludwigs-Universitat, 7800 Freiburg im Breisgau, W. Germany
Proc Natl Acad Sci USA; 79(13):4025-4029 1982

We have used antibodies against the synthetic peptide Lys-Arg-Ser-Arg-His-Phe, corresponding to the six COOH-terminal amino acids of the polyoma virus medium tumor (T) antigen, to purify the medium T antigen by affinity chromatography. Release of the medium T antigen from the anti-peptide antibody was achieved under mild conditions by using a large excess of the peptide in an isotonic buffer at neutral pH containing mixed detergents. This procedure yielded a 2,500-fold purification of the medium T antigen in a single step. The protein kinase activity associated with the medium T antigen was also released and was studied in this active state in solution. Sedimentation analysis showed that the bulk of the purified medium T antigen was in a monomeric form (Mr about 42,000) not associated with protein kinase activity. A small fraction of the medium T antigen was found in a rapidly sedimenting form (Mr about 200,000) that possessed protein kinase activity. (Author abstract) (26 Refs)

3. A COMPARATIVE STUDY ON ULTRASTRUCTURE AND IMMUNOLOGICAL PROPERTIES OF HUMAN PAPILLOMA VIRUS BEFORE AND AFTER FIXATION.

Kimura S, Harada R
Dept. Dermatolgy, Keio Univ. Sch. Medicine, Shinjuku-ko, Tokyo 160, Japan
J Dermatol (Tokyo); 9(2):87-91 1982

Effects of tissue processing on the ultrastructure and immunological properties of human papilloma virus (HPV) were studied comparatively by negative staining and immunofluorescence (IF) technique prior to and after fixation. The application of IF technique to deparaffinized sections of warts and other epidermal tumors is discussed. Structural alterations of HPV after processing with various fixatives are enlargement of capsomeres, increased diameter of particles, dim contour of particles, and destruction of particles. Results offered basic data which enable application of IF techniques to routinely prepared paraffin-embedded tissues of warts and other epidermal tumors. (12 Refs)

4. STABILITY AND COMPONENTS OF MATURE SIMIAN VIRUS 40.

Bina M, Beecher S, Blasquez V
Dept. Chemistry, Div. Biochemistry, Purdue Univ., West Lafayette, IN, 47907
Biochemistry; 21(13):3057-3063 1982

We have examined the stability of mature simian virus 40 (SV40) to changes in pH and have investigated the DNA-specific enzymatic activities that are released from SV40 virions. Our studies show that when SV40 virions are disrupted by the alkaline disruption method described by Brady et al, In addition to the capsid proteins, a DNA topoisomerase and a DNA endonuclease are released. Treatment with a reducing agent and divalent ion chelator is required for the release of both enzymes from the mature virions. Kasamatsu and Wu have previously isolated from SV40 virions a protein covalently linked to SV40 DNA under strongly denaturing conditions. Considering the known biochemical properties of DNA topoisomerases, we propose that the protein in Kasamatsu and Wu's isolated protein-DNA complex is the SV40-associated topoisomerase. In this work, we show that the topoisomerase is activated by Mg^{++} ions and does not require a high-energy cofactor to relax supercoiled DNA. On the other hand, the endonuclease is active at 37 C only in the presence of Mg^{++} ions. While the topoisomerase and the endonuclease activities are released from the virions near neutral conditions, the extent of dissociation of capsid proteins from SV40 chromosomes and the shape of subviral DNA-protein complexes depend on pH. At pH 10.4, the DNA-containing particles sediment at 60 S. At lower pH values, 9.8 and 9.2, the subviral nucleoprotein complexes sediment at 75 and 92 S, respectively. Below pH 9.0, the virus particles decay to a heterogeneous mixture of DNA-containing particles. The majority of the nucleoprotein complexes that result from disruption of the virions at pH 8.8 appears as highly compact SV40 chromatin. Electron microscopic observations and biochemical analysis suggest that a fraction of encapsidated SV40 chromatin seems to be deficient in histones or 'normal' nucleosomes. (Author abstract) (39 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

5. DIFFERENTIAL SUSCEPTIBILITY OF HUMAN CELLS TO TRANSFORMATION BY MURINE AND AVIAN SARCOMA VIRUSES.

Rhim JS, Trimmer R, Huebner RJ, Papas Ts, Jay G
NCI, NIH, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 170(3):350-358 1982

The susceptibility of human skin fibroblasts from patients with adenomatosis of the colon and rectum (ACR) and Gardner's syndrome and of human osteosarcoma clonal cells to Kirsten murine sarcoma virus (KiMSV) and Rous sarcoma virus (RSV) was investigated. Results obtained confirmed a previous report that skin fibroblasts from individuals genetically predisposed to colorectal cancer were preferentially transformed by KiMSV. The human osteosarcoma clonal cells infected with RSV showed altered morphology, increased growth rate, higher efficiency of colony formation in soft agar, growth of larger aggregates and growth in aggregate form above an agar base, and tumorigenicity in nude mice. The transformed cells produced neither RNA-dependent DNA polymerase nor type C virus particles; however, the transformed cells contained RSV CF antigen and a rescuable infectious virus. The transformed cells also contained an RSV transformation specific protein p60src-associated kinase activity. (22 Refs)

6. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.

Weinberg RA

Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139

Adv Cancer Res; 36:149-163 1982

The value of experiments involving the process of gene transfer, termed transfection, in resolving questions concerning the role of DNA damage in oncogenic transformation is discussed. Topics reviewed include a model of cellular oncogenes; the retrovirus-associated oncogenes; oncogenes of cells transformed by chemical carcinogens; the transforming genes in 3-methylcholanthrene-transformed cells; types of transformed cells yielding focus-induced DNA; the multiplicity of human oncogenes; and analogies between virus-and non-virus-induced cellular oncogenes. The process of activation of oncogenes, the role of oncogenes in carcinogenesis and maintenance of phenotype, and the proteins encoded by activated oncogenes are discussed. It is unlikely that activation of a cellular oncogene is the only necessary alteration occurring during the conversion of a normal cell into a tumor cell; other genetic and epigenetic controls are probably involved in realization of the oncogenic phenotype. Experiments to date suggest, however, that a multistep process is not involved, and that a single genetic determinant is able to effect the conversion of the recipient cell from normal fibroblast into highly tumorigenic fibrosarcoma cell. It is possible that recipient cells in such experiments already have undergone many necessary predisposing steps, and that only the final alteration is provided by the transfected oncogene. (34 Refs)

7. INTERACTION OF EPSTEIN-BARR VIRUS WITH LEUKAEMIC B CELLS IN VITRO. II. CELL LINE ESTABLISHMENT FROM PROLYMPHOCYTIC LEUKAEMIA AND FROM WALDENSTROM'S MACROGLOBULINAEMIA.

Finerty S, Rickinson AB, Epstein MA, Platts-Mills TA

Dept. Pathology, Medical Sch., Univ. Bristol, Bristol, England

Int J Cancer; 30(1):1-7 1982

Leukemic B-cell populations were prepared from six patients with high-count prolymphocytic leukemia (PLL) as well as from one patient with Waldenstrom's macroglobulinemia (WM) in frankly leukemic phase, and their response to in vitro Epstein-Barr (EB) virus infection was monitored in terms of expression of the virus-associated nuclear antigen EBNA and of virus-induced transformation to continuous cell lines. The individual leukemic populations, tested on several occasions, gave reproducibly different responses one from another which were not obviously related to differences either of surface immunoglobulin phenotype or of immunoglobulin secretor status in vivo. After infection, four out of six PLL populations showed either transient or a more persistent expression of EBNA, always involving a minority of the cells, with no evidence of any virus-induced transformation up to 6 wk. In contrast, two out of six PLL samples as well as the WM sample rapidly gave rise to EBNA-positive cell lines which, on the evidence both of restricted immunoglobulin class expression and of abnormal marker chromosomes, were clearly derived from the leukemic cells. Further comparative studies of such leukemic B-cell populations may help to define host cell components necessary for the triggering of EB-virus-induced cellular transformation. (Author abstract) (32 Refs)

8. A MONOCLONAL IMMUNOBLASTIC SARCOMA IN DONOR CELLS BEARING EPSTEIN-BARR VIRUS GENOMES FOLLOWING ALLOGENEIC MARROW GRAFTING FOR ACUTE LYMPHOBLASTIC LEUKEMIA.

Schubach WH, Hackman R, Neiman PE, Miller G, Thomas ED

Div. Medical Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104

Blood; 60(1):180-187 1982

A patient undergoing marrow grafting for acute lymphoblastic leukemia from his partially HLA-mismatched sister displayed a widely disseminated immunoblastic sarcoma at autopsy. The tumor was monoclonal by immunoglobulin light-chain staining. Blot hybridization analysis, using a cloned highly polymorphic locus in human DNA as a probe, showed the tumor to be of donor-cell origin. Cytogenetic analysis also demonstrated donor-cell origin. Blot hybridization analysis demonstrated Epstein-Barr virus (EBV) genomes in the tumor. By contrast, reexamination of material from a previously reported case of a donor-type relapse showed no evidence of EBV DNA. In neither case was there evidence of cytomegalovirus DNA. This study documents the association of EBV with a malignant, monoclonal B-cell lymphoma arising in a marrow graft recipient. We conclude that DNA restriction fragment length polymorphisms can be used to prove the origin (donor or host) of neoplastic relapse following allogeneic marrow grafting. Further, cell types different from those of the original leukemia may be involved. (Author abstract) (35 Refs)

9. HLA-DR TYPING OF FETAL HUMAN SPLEEN AND LIVER LYMPHOBLASTOID CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Mandel TE, Jack I, Tait BD

Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia

Transplantation; 34(1):50-53 1982

Because few HLA-DR-positive cells are present in the spleen and liver, full HLA typing cannot be performed. However, B lymphocyte precursors can be transformed with Epstein-Barr virus to produce lymphoblastoid cells which express HLA-A, B, and DR antigens. Successful transformation was achieved, usually with spleen and liver, in nine fetuses aged from 15 to 18 wk, mostly within 7 to 14 days of initiation of the cultures. Spleen-derived lymphoblasts were more suitable for typing because of their greater homogeneity and higher viability. Tissues from two 13-week fetuses from prostaglandin-induced abortions and from a spontaneously aborted 22-week fetus could not be transformed. This is probably attributable to prolonged ischemia before the tissues were obtained but, in the 13-week fetuses, absence of B lymphocyte precursors was not excluded. HLA-DR typing may be useful in obtaining well matched donor-recipient pairs in fetal pancreatic islet transplantation. (Author abstract) (33 Refs)

10. INDUCTION OF SYNTHESIS OF EPSTEIN-BARR VIRUS DNA AND VIRUS-SPECIFIC POLYPEPTIDES BY TUMOR PROMOTER IS ENHANCED BY NON-PROLIFERATIVE STATE OF CELLS (MEETING ABSTRACT).

Lin JC, Smith MC, Pagano JS, Feighny RJ
Cancer Research Center, University of North Carolina, Chapel Hill, NC, 27514
Proc Am Assoc Cancer Res; 23:2 1982

TPA (12-0-tetradecanoylphorbol-13-acetate) is a potent inducer of Epstein-Barr Virus (EBV) gene expression. The magnitude of activation of latent EBV genome by TPA depended upon the physiological state of the cells when they were exposed to drug. While TPA was able to induce EBV genome replication in P3HR-1 cells in all phases of growth, the most dramatic increase in viral genome copies per cell occurred in nonproliferative cells as opposed to cells in exponential growth. Early antigen (EA) synthesis in nonproliferative Raji cells activated by TPA increase 300-fold in contrast to only 100-fold increase in exponentially growing cells treated with TPA. The marked enhancement in activation of latent EBV genomes and marked reduction in cellular protein synthesis in nonproliferative cells treated with TPA makes it possible for direct detection of virus-specific polypeptides associated with activation. Analysis of polypeptides synthesized in TPA - induced P3HR-1 cells by immunoprecipitation indicated that polypeptides of 155K, 140K, 90K, and 78K were induced by TPA, whereas 145K, 120K, 92K, 80K, 75K, 72K, 68K, 65K and 50K were polypeptides present in spontaneously induced P3HR-1 cells not treated with TPA. At least eleven polypeptides (90K, 80K, 75K, 52K, 46K, 45K, 43K, 40K, 38K, 35K, and 33K) were clearly detected in TPA-induced Raji cells. The insensitivity of these polypeptides to acyclovir and their appearance paralleling EA induction lead us to conclude that at least some are components of EA. (no Refs)

11. THE INFECTIOUS MONONUCLEOSIS DOWNEY CELL POPULATION AND PAUL-BUNNELL ANTIGEN/ANTIBODY (MEETING ABSTRACT).

Fjelde A, Robolt O, Kellam J, Bennett P
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:1079 1982

In conjunction with previous studies with F Milgrom and K Kano, of the Paul-Bunnell (PB) heterophile system, in which we demonstrated presence of PB antigen in (40%) human lymphoma-leukemia (LL) spleens, we studied the abnormal Downey cells found in IM along with PB antibodies, the antigen to which is considered to be unknown. We postulated that PB antigen is a neo-antigen arising as a result of B cell infection and is related to the benign nature of IM. Paul and Bunnell described PB antibody in 1932 and Downey and McKinley described IM lymphocytes in 1923. Since then the abnormal (Downey) lymphocytes and PB antibody have been considered diagnostic for IM. Using acute phase IM blood, we employed cell separation and identification techniques, to obtain purified or enriched cell populations. We found, in absolute values, a low increase in the B cell population and a high increase of T cells, depending on the lymphocytes/mm3. We were unable to detect PB antigen in IM peripheral blood lymphocytes. EBV (Epstein-Barr virus) believed to cause IM, infects B cells which during maturation develop virus receptor sites and in culture proliferate as established lines. T cells have finite life unless the culture media contains a growth factor. In vivo the Downey cell population consists of 'reactive' T cells, giving rise to the terminology 'self-limiting leukemia' to IM. A double immune system, the PB heterophile and the EBV, exists in IM patients. PB antibodies disappear during convalescence, but PB antigen is found in LL patients. (no Refs)

12. LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: ABILITY OF EXTRACTS TO REMOVE O6METHYLGUANINE FROM ALKYLATED DNA (MEETING ABSTRACT).

Setlow RB, Waldstein EA, Cao EH, Miller ME, Cronkite EP
Biology and Medical Departments, Brookhaven National Laboratory, Upton, NY, 11973
Proc Am Assoc Cancer Res; 23:51 1982

O6methylguanine (O6MeGua) is a presumptive mutagenic and carcinogenic product in DNA treated in vivo or in vitro with N-nitroso compounds. Normal human cell lines (mer+) remove 6MeGua from their DNA whereas an appreciable number of tumor and virus transformed cell lines are deficient (mer-) in this respect. We examined the O6MeGua-removing capacity of lymphocytes from 6 patients with chronic lymphocytic leukemia (CLL) and one with polycythemia vera (PV). Unexpectedly lymphocytes from CLL patients, mainly B type, appeared to be super mer+, showing an increased capacity to remove O6MeGua when compared to B type lymphocytes of normal individuals. The activity per cell increases with the WBC and the stage of the disease. Unlike normal lymphocytes, incubation of lymphocytes from CLL patients with or without phytohemagglutinin results in a decrease rather than an increase in activity. The activity from CLL patients, as in normal lymphocytes, acts in a stoichiometric fashion and transfers about 80% of the methyl groups to a cysteine moiety of an acceptor protein. The number of acceptor molecules per cell in lymphocytes of CLL patients is estimated to range between 94,000 and 240,000-4 to 10 fold higher than in normal B type lymphocytes. The estimate for lymphocytes from PV patients is about 40,000 which falls in the range of 14,000-110,000 per cell estimated for unstimulated lymphocytes, mostly T type, of normal individuals. (2 Refs)

13. CHARACTERIZATION OF AN AMINO ACID FUCOSIDE OF NORMAL AND SV40-TRANSFORMED HUMAN EMBRYONIC LUNG CELLS.

Morton PA, Klinger MM, Steiner SM
(c/o Steiner) T. H. Morgan Sch. Biological Sciences, Univ. Kentucky, Lexington, KY, 40506
Cancer Res; 42(8):3022-3027 1982

The incorporation of radioisotopically labeled fucose into a prominent fucosylated component, ie, fucose-labeled amino acid fucoside 4c (FL4c), of human embryonic lung cells is markedly decreased in cell lines derived from human tumors. In the current study, we have extended the above observations by examining more closely related normal and transformed human cells, eg, W138 cells and SV40-transformed W138 cells. We have found that the level of radioisotopically labeled fucose incorporated into FL4c of the SV40-transformed human embryonic lung cells is dramatically reduced as compared to their normal counterpart cells. Additionally, we have chemically characterized FL4c. FL4c was purified from monkey tissues using a combination of gel filtration chromatography, ion-exchange chromatography, and preparative thin-layer chromatography. Analysis of this material was accomplished by amino acid analyzer and by gas-liquid chromatography; fucose, glucosamine, and aspartic acid in molar ratios of approximately 1.0:1.0:1.0 were observed. Furthermore, alpha-L-fucosidase treatment of [3H]fucose-labeled FL4c revealed that the fucose was alpha-linked and in a terminal position. Similar treatment of [3H]glucosamine-labeled FL4c yielded a component that cochromatographed with N-acetylglucosaminylasparagine. The combined results of the structural studies are consistent with the structure of FL4c being alpha-fucosyl-N-acetylglucosaminylasparagine. (Author abstract) (25 Refs)

14. FUSION-INDUCED DIFFERENTIATION OF SV40-INFECTED HUMAN KERATINOCYTES.

Steinberg ML, Defendi V

Dept. Pathology, New York Univ. Medical Center, New York, NY, 10016

Exp Cell Res; 139(2):369-375 1982

Cells in cultures of human keratinocytes infected by the oncogenic virus, SV40, were fused by exposure to polyethylene glycol (PEG). Fusion induced differentiation of the infected cells within 1-2 days, as measured by staining with orange G/acid fuchsin and by the production of cornified envelopes. The extent of induced differentiation was found to be correlated with the degree of multinucleation. The inductive effect of fusion was manifest during the early serial passages post-infection, but was eventually lost as the keratinocytes became increasingly transformed over time. (Author abstract) (18 Refs)

15. TUMORIGENICITY OF SV40-TRANFORMED HUMAN CELLS IN IMMUNODEFICIENT MICE (MEETING ABSTRACT).

Choi KH, Kahn P, Shin SI

Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, 10461

Proc Am Assoc Cancer Res; 23:95 1982

Neoplastic transformation of mammalian cells in vitro by the simian papova virus SV40 is widely used as an experimental model of viral oncogenesis. It was shown prevously that rodent cells transformed by SV40 to the anchorage-independent state form progressively growing tumors in athymic nude mice. In contrast, human cells similarly transformed by SV40 rarely form tumors in this host. To determine whether their failure to form tumors is due to rejection by a thymus-independent mechanism in the athymic host, the tumorigenicity of a cloned SV40-transformed human cell line designated SV80 was examined in BALB/c nude mice under a variety of conditions. We found that SV80 cells can grow as tumors if they are injected sc into immature CBA/N nude mice or if they are repeatedly injected ip into newborn BALB/c nude mice over a period of 3 weeks. In the latter case, all mice (8/8) developed widespread metastatic nodules in the peritoneal and thoracic cavities. Somatic cell hybrids produced by fusing SV80 cells with a highly tumorigenic clone of HeLa cells were also found to be nontumorigenic in BALB/c nude mice, but hybrid cells not expressing the virus-coded tumor (T) antigens were tumorigenic in the same host. These and additional related data support the hypothesis that at least some human cells transformed by SV40 are inherently tumorigenic, and that these cells are unable to form growing tumors in nude mice because of the existence of a thymus-independent tumor rejection mechanism. (no Refs)

16. DIFFERENTIAL CELL CYCLE ARREST OF NORMAL VERSUS TRANSFORMED CELLS BY THE PROTEIN SYNTHESIS INHIBITOR ANGUIDINE (MEETING ABSTRACT).

Hromas R, Barlogie B, Drewinko B, Ho DH

The University of Texas Cancer Center, M.D. Anderson Hospital and Tumor, Institute Houston, TX

Proc Am Assoc Cancer Res; 23:811 1982

Anguidine induces a reversible and universal cell cyle arrest in Chinese hamster ovary cells. This cytotoxtic effect is accompanied by a reduction in the cytotoxicity of subsequently administered cytosine arabinoside (ara-C), 5-fluorouracil, adriamycin, hydroxyurea, and hyperthermia. To determine whether this cycle arrest could be exploited therapeutically, we examined the possiblity that anguidine could exert a differential suspension of cycle traverse in normal vs transformed cells. In Balb/C and Swiss 3T3 cell lines, anguidine induced cycle arrest at one-half the concentration needed to produce a similar effect in SV-3T3 cells. By comparison, WI38 cells were blocked from progressing through the cell cycle at one-tenth the concentration of anguidine required to inhibit cycle progression of WI38 VA13 cells (SV-40 transformant). In experiments combining anguidine and ara-C or adriamycin, there was a selective protection of WI38 but not of WI38 VA13 cells related to the preferential cell cycle arrest of WI38 cells. Since human tumors often proliferate at a slower rate than such normal tissue as gut epithelium and bone marrow, it is possible that anguidine could be used clinically to protect normal tissue from the dose limiting side effects of some chemotherapeutic agents. (no Refs)

17. HYBRIDS FROM FUSION OF TUMOR CELLS WITH NORMAL AND SV40 TRANSFORMED HUMAN FIBROBLASTS HAVE A FINITE IN VITRO LIFESPAN (MEETING ABSTRACT).

Pereirasmith OM, Smith JR

W. Alton Jones Cell Science Center, Inc., Old Barn Road, Lake Placid, NY, 12946

In Vitro; 18(3,part2):283 1982

Human diploid cells have finite division potential in vitro, while tumor derived and virally transformed human cells divide indefinitely. To investigate the processes leading to the acquistion of indefinite proliferation, we have studied the proliferative potential of hybrids from normal x tumor and tumor x SV40 transformed cell fusions. We have previously found that 30-50% of hybrids from normal x SV40 transformed cell fusions were capable of extensive division (greater than 10 PD). However, when normal fibroblasts were fused with various human tumor cell lines, only 3% or less of the hybrids were able to divide extensively. It is therefore possible that different processes lead to indefinite proliferation in the SV40 vs tumor derived cell lines. If this is the case, tumor x SV40 transformed cell fusions might yield hybrids with finite lifespan. Fusion of an SV40 transformed human fibroblast with various tumor cell lines yielded 20% or fewer hybrids capable of extensive proliferation. When the tumor line was derived from a carcinoma, glioma or osteosarcoma, these hybrids eventually stopped dividing. Fusion with a fibrosarcoma, however, yielded hybrids that achieved at least 100 PD. These results demonstrate the dominance of the finite lifespan phenotype in normal x immortal cell fusions and suggest that different indefinitely proliferating lines arise due to loss of different specific regulatory functions. (no Refs)

18. CYTOTOXICITY AND DNA CROSSLINKING IN NORMAL AND TRANSFORMED HUMAN CELLS EXPOSED TO 1-(2-FLUOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (FCNU) (MEETING ABSTRACT).

Sharkey NA, Erickson LC, Kohn KW, Oliverio VT
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:642 1982

FCNU, the fluoro analogue of CCNU, is as active as CCNU (lomustine) or other chloroethylnitrosoureas (CNU) against murine tumors. It differs from the CNU's, however, in that it produces much less DNA interstrand crosslinking (ISC). We have recently reported that ISC and cytotoxicity induced by CNU in human tumor cell depend on the Mer (methylation repair) phenotype. We now report the effects of FCNU on ISC and cytotoxicity in normal human fibroblasts (IMR-90) (Mer+) and SV-40 transformed human fibroblasts (VA-13) (Mer-). In cytotoxicity experiments, twice the drug concentration was required to effect a similar cell kill in IMR-90 as compared to VA-13. When the cell lines were analyzed by alkaline elution, comparable levels of DNA-protein crosslinking (DNP) were observed in both cell lines immediately after drug exposure, (DNP) increased in both lines over the next 24 hours, and decreased slowly in the subsequent 48 hour period. DNA interstrand crosslinking was detected in VA-13 but not in IMR-90 cells. However, unlike the chloroethylnitrosoureas which produce DNA interstrand crosslinks in the 6-12 hour period following drug treatment, interstrand crosslinks produced by FCNU in VA-13 cells were not detected until 48 hours after drug exposure. FCNU inhibited the proliferation of VA-13 cells as early as 24 hr after treatment, ie, before ISC was detected. (1 Ref)

19. MALIGNANT TRANSFORMATION OF HUMAN EMBRYO RETINOBLASTS BY CLONED ADENOVIRUS 12 DNA.

Byrd P, Brown KW, Gallimore PH
Cancer Res. Campaign Laboratories, Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England
Nature; 298(5869):69-71 1982

Isolation of a recombinant plasmid (pAsc2)-trans human embryo retinoblast (HER) cell line that contains many copies of the adenovirus Type 12 (Ad 12) transforming region, expresses virus-specified proteins, and following inoculation into athymic mice, forms tumors which resemble retinoblastomas is described. Primary cultures of human retinoblasts were transfected with pAsc2, and one transformed focus, identified 45 days after transfection, was isolated and established as a continuous cell line. The cell line has been designated Ad 12 HER1 and was the first reported Ad 12-transformed human cell line. Cytogenetic analysis revealed a pseudotetraploid human karyotype. The Ad 12 HER1 cell line was grown beyond the thirty-sixth tissue culture passage level and at no time has its growth entered a crisis phase. When Ad 12 HER1 cell DNA was digested with the restriction endonucleases BglII or SstI and subjected to Southern blotting analysis using P-labeled Ad 12 EcoRI-C DNA fragments as a probe, Ad 12 sequences were found on many DNA fragments whose sizes ranged from greater than 12 kilobase pairs (kb) to 2.2 kb. As these enzymes cleave host DNA sequences only, each fragment represented a separate insert of pAsc2 sequences. Results suggested that Ad 12 HER1 cells contain intact, integrated copies of viral and vector sequences and it is likely that some of the inserts contain tandem repeats of the entire recombinant plasmid. Histological analysis of the Ad 12 HER1-induced tumors showed them to consist of clusters of small cells with many mitotic figures characteristic of poorly differentiated human retinoblastomas. (29 Refs)

20. A HUMAN HEPATOMA CELL LINE (PLC/PRF/5) PRODUCES LUNG METASTASES AND SECRETES HBSAG IN NUDE MICE.

Sattler FR, Paolucci S, Kreider JW, Ladda RL
500 University Drive, Hershey, PA, 17033
Eur J Cancer Clin Oncol; 18(4):381-389 1982

PLC/PRF/5 is a human liver cancer cell line which synthesizes hepatitis B virus surface antigen (HBsAg). These cells produced tumor in 6 of 8 (75%) congenitally athymic nude mice at 13 of 28 subcutaneous injection sites and in 13 of 14 (93%) mice inoculated intraperitoneally. Tumors were successfully transplanted to four of six additional nude mice. Tumor growth was rapid. Growth of cephalad tumors was significantly greater than for caudal tumors (0.39 mm/day vs 0.28 mm/day). Microscopic examination of tumors showed moderately well-differentiated hepatocellular carcinoma. Foci of identical cells were present in pulmonary veins in 7 of 14 tumor-bearing animals. Tumor cell karyotype was identical with that of PLC/PRF/5 cells. In addition, HBsAg was detectable in high titer in animals with extensive tumor. Biological features of PLC/PRF/5-induced tumors in nude mice appeared to closely resemble human hepatocellular carcinoma. Moreover, HBsAg may provide a marker of tumor growth. (Author abstract) (24 Refs)

VIRUS REPLICATION AND EXPRESSION

21. ISOLATION AND CHARACTERIZATION OF THE GROWTH-STIMULATING FACTOR IN SUPERNATANTS OF HERPES SIMPLEX VIRUS TYPE 2 INFECTED CELLS.

Reiss-Gutfreund RJ, Letnansky K, Desser H
Inst. Cancer Res., Borschkegasse 8a, A-1090 Vienna, Austria
Oncology; 39(5):319-324 1982

Lytic infection of CV1 cells with herpes simplex virus Type 2 does not stimulate ornithine decarboxylase activity and there is no correlation between polyamines and a growth-stimulating factor (GSF) which is present in the supernatant of the cultures. The factor was partially purified by gel filtration on Sephadex G-50 and polyacrylamide gel electrophoresis. Gel filtration as well as dialysis through membranes with different pore diameters indicated a mol wt between 3,500 and 10,000 daltons. GSF is not extracted from aqueous solutions by diethyl ether. The activity is partially sensitive to trypsin digestion and is completely destroyed by periodate oxidation. These results suggest that GSF is a glycoprotein or a glycopeptide whose mitogenic activity resides mainly in the sugar moiety. (Author abstract) (24 Refs)

22. DEFINITION OF A SERIES OF STAGES IN THE ASSOCIATION OF TWO HERPESVIRAL PROTEINS WITH THE CELL NUCLEUS.

Knipe DM, Spang AE
Dept. Microbiology and Molecular Genetics, Harvard Medical Sch., Boston, MA, 02115
J Virol; 43(1):314-324 1982

We examined the kinetics and the nature of the association of two herpes simplex virus proteins, the major DNA-binding protein (ICP8) and the major capsid protein (ICP5), with the nuclei of infected cells. We defined a series of stages in the association of the ICP8 protein with the cell nucleus. (i) Immediately after synthesis, the protein was found in the cytoplasmic fraction but associated rapidly with the crude nuclear fraction. (ii) The initial association of ICP8 with the crude nuclear fraction was detergent sensitive but DNase resistant. (iii) At intermediate times, a low level of an intermediate form was observed in which the association of ICP8 with the nuclear fraction was resistant to both detergent and DNase treatment. The protein may be bound to the nuclear matrix at this stage. Inhibition of viral DNA synthesis caused the DNA-binding protein to accumulate in this form. (iv) At late times during the chase period, the association of ICP8 with the cell nucleus was resistant to detergent treatment but sensitive to DNase treatment. Our results argue that at this stage ICP8 was bound to viral DNA. Thus, nuclear association of the DNA-binding protein did not require viral DNA replication. More important is the observation that there is a series of stages in the nuclear association of this protein, and, thus, there may be a succession of binding sites for this protein in the cell during its movement to its final site of action in the nucleus. The major capsid protein showed some similar stages of association with the cell nucleus but the initial association with the nucleus followed a lag period. Its early association with the crude nuclear fraction was also detergent sensitive but was resistant to detergent treatment at later times. Its association with the cell nucleus was almost completely resistant to DNase treatment at all times. Inhibition of viral DNA replication blocked the nuclear transport of this protein. Thus, these two viral proteins share some stages in nuclear transport, although their requirements for nuclear association are different. (27 Refs)

23. POLYSOME-ASSOCIATED PROTEINS IN HERPES SIMPLEX VIRUS-INFECTED CELLS.

Bartkoski MJ
Dellen Lab., Omaha, NE, 68134
J Virol; 43(1):357-360 1982

In the cytoplasm of eucaryotic cells, mRNA is associated with proteins. These mRNA-protein complexes, termed messenger ribonucleoprotein (mRNP) particles, are divided into two functional classes. The first class contains free (non-ribosome-associated) mRNPs which have been termed informosomes by others. The second class of mRNPs, those associated with polysomes, are actively engaged in protein synthesis and are termed polysomal mRNPs. The experiments described in this paper examined the proteins associated with polyribosomes in uninfected and herpes simples virus Type 1-infected cells. The data indicate that after infection with herpes simplex virus Type 1, specific changes occur in the proteins which normally are found associated with these polysomal mRNPs. These changes include both the appearance of new and possibly virus-specific proteins and the loss of normal host-specific proteins. The relationship of these changes to the patterns of protein synthesis in these cells is also discussed. (Author abstract) (36 Refs)

24. EPSTEIN-BARR VIRUS RNA VIII. VIRAL RNA IN PERMISSIVELY INFECTED B95-8 CELLS.

Hummel M, Kieff E
(c/o Kieff) Dept. Biology, Medicine, Section Infectious Diseases, Kovler Viral Oncology Lab., Univ. Chicago, Chicago, IL, 60637
J Virol; 43(1):262-272 1982

More than 50 RNAs expressed by Epstein-Barr virus late in productive infection have been identified. B95-8 infected cells were induced to a relatively high level of permissive infection with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate. Polyadenylated RNAs were extracted from the cell cytoplasm, separated by size on formaldehyde gels, transferred to nitrocellulose, and hybridized to labeled recombinant Epstein-Barr virus DNA fragments. Comparison of RNAs from induced cultures with RNAs from induced cultures also treated with phosphonoacetic acid to inhibit viral DNA synthesis identifies two RNA classes: a persistent early class of RNAs whose abundance is relatively resistant to viral DNA synthesis inhibition and a late class of RNAs whose abundance is relatively sensitive to viral DNA synthesis inhibition. The persistent early and late RNAs are not clustered but are intermixed and scattered through most of segments UL and US. The cytoplasmic polyadenylated RNAs expressed during latent infection were not detected in productively infected cells, indicating that different classes of viral RNA are associated with latent and productive infection. Non-polyadenylated small RNAs originally identified in cells latently infected with Epstein-Barr virus are expressed in greater abundance in productively infected cells and are part of the early RNA class. (Author abstract) (53 Refs)

25. FILAMENTOUS STRUCTURES ASSOCIATED WITH EPSTEIN-BARR VIRUS-INFECTED CELLS.

Moore CL, Griffith JD, Shaw JE
(c/o Shaw) Cancer Res. Center, Dept. Bacteriology and Immunology, Univ. North Carolina, Chapel Hill, NC, 27514
J Virol; 43(1):305-313 1982

After the onset of Epstein-Barr virus DNA and protein synthesis 10 h after superinfection of Raji cells (a cell line containing Epstein-Barr virus DNA but not producing virus), filamentous structures 25 nm in diameter and 0.2 to 1.4 um in length could be detected in the cell cytoplasm by electron microscopy. These structures banded in metrizamide gradients with viral DNA and proteins, but at a density different from that of virions or nucleocapsids. These filaments, enriched in a 155,000-dalton protein similar in size to a major nucleocapsid protein of Epstein-Barr virus, may represent intermediates in viral nucleocapsid assembly. (Author abstract) (37 Refs)

26. A SMALL SUBCLASS OF SV40 T ANTIGEN BINDS TO THE VIRAL ORIGIN OF REPLICATION.

Scheller A, Covey L, Barnet B, Prives C
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
Cell; 29(2):375-383 1982

We examined the affinities of SV40 large T antigen for unique viral DNA sequences by binding SV40 Bst NI DNA fragments in extracts of infected or transformed cells, and then immunoprecipitating the T antigen-DNA complex. The G fragment, which spans the viral origin of replication (ori) was quantitatively bound to T antigen. A T-antigen-specific monoclonal antibody (Mcl 7), which recognized only 5%-10% of the T antigen from infected or transformed cells, immunoprecipitated the majority of the ori-binding activity. This suggests that only a minor subclass of wild-type T antigen is active in binding to the origin. C6 cells contain a replication-defective mutant T antigen that when tested in the DNA-binding immunoassay, showed no affinity for the ori fragment. Mcl 7 not only failed to immunoprecipitate ori binding in C6 cells, but also did not detect any labeled C6 T antigen whatever. Thus Mcl 7 recognizes an immunologically distinct subset of wild-type T antigen that comprises the origin-binding form of the viral protein, which is absent in the C6 T antigen population.

Mcl 122, which recognizes a 53 kilodalton host protein that complexes with T antigen, immunoprecipitated ori-binding activity from extracts of infected or transformed cells, but not from C6 cells. Thus wild-type T antigen can bind ori sequences even when complexed to the host protein. These data suggest that T antigen consists of different subpopulations with different functions. (Author abstract) (48 Refs)

27. CV-1 CELLS RELEASE PROTEINS THAT FACILITATE INFECTION BY SIMIAN VIRUS 40 AND ECHOVIRUS 6.

Righthand VF, Bagshaw JC

Dept. Immunology and Microbiology, Wayne State Univ. Sch. Medicine, Detroit, MI, 48201

Arch Virol; 73(1/2):55-66 1982

Uninfected simian cells (CV-1) produce two different proteins, one of which enhances the infectivity of echovirus 6 and the other enhances the infectivity of SV40 in less susceptible cells. The enhancers are released by metabolizing cells into the culture medium. The SV40 enhancer protein is larger and less acidic than the echovirus enhancer. The SV40 enhancer protein can be dissociated into two subunits with apparent mol wt of 42,000 and 24,000. The echovirus enhancer protein consists of two subunits with apparent mol wt of 28,000 and 31,000. Electrophoretically purified enhancer proteins interact with virions and retain their biological activities and viral specificities. The SV40 enhancer stimulates expression of SV 40-T antigen under conditions in which untreated virus does not initiate expression of T antigen. This result and the observation that the enhancers do not increase the infectivity of the nucleic acids of their respective viruses suggest that the enhancers act either at the stage of penetration or uncoating. (Author abstract) (13 Refs)

28. ANALYSIS OF YABA TUMOR POXVIRUS-INDUCED PROTEINS IN INFECTED CELLS BY TWO-DIMENSIONAL GEL ELECTROPHORESIS.

Vafai A, Rouhandeh H

(c/o Rouhandeh) Lab. Molecular and Cancer Virology, Dept. Microbiology, Southern Illinois Univ. at Carbondale, Carbondale, IL, 62901

Virology; 120(1):65-76 1982

Lack of inhibition of host protein synthesis by Yaba tumor poxvirus and comigration of viral and host proteins did not interfere with high resolution of virus-induced proteins when two-dimensional gel electrophoresis was employed. At total of 84 virus-induced proteins, 44 structural and 40 nonstructural, comprising 62.9% of the coding capacity of Yaba virus DNA were detected. These proteins may be further categorized in two classes: early, synthesized in the presence of DNA inhibitor, Ara-c; and late, beginning at 6 hr pi with the bulk of viral protein synthesis occurring later than 30 hr pi The rate of synthesis of viral proteins fell into two patterns: Group A, in which the rate of synthesis decreased; and, Group B, in which the rate of synthesis increased after the initial appearance of the protein. (Author abstract) (35 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

29. HOST CELL REACTIVATION BY EXCISION REPAIR IS ERROR-FREE IN HUMAN CELLS.

Lytle CD, Nikaido O, Hitchins VM, Jacobson ED

Bureau Radiological Health, FDA, HSS, Rockville, MD, 20857

Mutat Res; 94(2):405-412 1982

The extent of viral mutagenesis was examined during the growth of UV-irradiated macro-plaque strain of herpes simplex virus Type 1 in human skin fibroblasts which lack excision repair or have reduced post-replication repair. Survival curves of the UV-irradiated virus were determined on confluent monolayers of cells at the same time that virus was grown in those cells for production of progeny virus. Over the range of survival investigated, the dose-reduction factor for normal cells was 0.82 (0.79-0.84), indicating that approx 80% of the potentially lethal lesions were repaired in normal cells but not in xeroderma pigmentosum (complementation group A; XPA) cells. Over the range of doses used, the virus mutation frequency was linearly related to dose when the irradiated virus was grown in XPA or normal cells with slopes of 7.9 x 10(-5) square meter/Joule (m2/J) and 1.8 x 10(-5) m2/J, respectively. Virus grown in the xeroderma pigmentosum (XP) variant cells had a mutation frequency that increased as the dose squared. The mutagenesis at different numbers of lethal hits was similar for virus grown in XPA and normal cells. The two-component nature of the mutagenesis vs lethal-hit curves (for XPA and normal cells) was apparently a result of the combination of linear mutagenesis with two-component survival. Results indicated that in human cells host cell reactivation by excision repair is primarily an error-free process. (19 Refs)

30. IN VITRO TRANSCRIPTION OF TWO EPSTEIN-BARR VIRUS SPECIFIED SMALL RNA MOLECULES.

Jat P, Arrand JR

Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England

Nucleic Acids Res; 10(11):3407-3425 1982

Cloned DNA from the EcoRI J fragment of EBV has been used as template for in vitro transcription experiments using cell-free extracts prepared from HeLa or KB cells. Two EBV specific RNAs each about 175 bases in length were synthesized and nuclease S1 mapping experiments determined that these in vitro products corresponded precisely to the in vivo species obtained from Raji cells. Thee two RNA molecules are transcribed by RNA polymerase III and in common with other pol III-synthesized RNAs the coding sequences contain intragenic control regions. The relative abundance of the two RNAs synthesized in vitro differs from that observed in vivo. (Author abstract) (48 Refs)

31. ORGANIZATION OF THE EPSTEIN-BARR VIRUS DNA MOLECULE. II. FINE MAPPING OF THE BOUNDARIES OF THE INTERNAL REPEAT CLUSTER OF B95-8 AND IDENTIFICATION OF ADDITIONAL SMALL TANDEM REPEATS ADJACENT TO THE HR-1 DELETION.

Hayward SD, Lazarowitz SG, Hayward GS
Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
J Virol; 43(1):201-212 1982

We used cloned BamHI fragments from Epstein-Bar virus strain B95-8 [EBV(B95-8)] DNA to obtain detailed restriction maps of the region of the genome adjacent to the large internal repeat cluster. These maps together with the results of hybridization experiments using a 3.1-kilobase repeat probe defined more precisely the location of the junctions between the internal repeat cluster and the flanking unique-sequence DNA. On one side (UL), the repeat sequences extended 600 +-80 base pairs (bp) into BamHI-Y; on the other side (Us), they extended 1,300 +-200 bp into BamHI-C. Therefore, EBV(B95-8) DNA contained a nonintegral number of 3.1-kilobase repeat units, namely, 12.6 copies. The mapping studies also revealed a second series of internal tandem repetitions in EBV(B95-8) DNA located within the BamHI-H fragment. This cluster comprised 11 copies of a 135-bp repeat unit which contained a single site for the NotI restriction endonuclease. Hybridization to these cloned EBV(B95-8) fragments using total EBV(HR-1) DNA as probe indicated that the deletion in EBV(HR-1) removed all 3,000 bp of unique-sequence DNa which lay between the large 3.1-kilobase and the small 135-bp repeat clusters. Thus, the deletion which destroyed the transforming ability in the EBV(HR-1) virus was bounded on either side by tandem repetitions. (Author abstract) (25 Refs)

32. RESCUE OF SV40 FOLLOWING TRANSFECTION OF TC7 CELLS WITH CELLULAR DNAS CONTAINING COMPLETE AND PARTIAL SV40 GENOMES.

Lipotich G, Moyer MP, Moyer RC
Thorman Cancer Res. Lab., Trinity Univ., San Antonio, TX, 78284
MGG; 186(1):78-81 1982

Infectious SV40 virions could be rescued from permissive TC7 cells within one to three subcultures following cotransfection with two cellular DNAs, each containing a complementary portion of the SV40 genome. SV40 virions could also be rescued by transfection of TC7 cells with cellular DNAs from a variety of SV40 transformed cells containing complete genome equivalents but not from cells containing subgenomes alone or defective genomes. Infectious virus was not rescued if the transfecting DNA species was treated with DNAase or if the DEAE-dextran pretreatment of the recipient cells was omitted. (Author abstract) (16 Refs)

33. DELETION MUTANTS WHICH AFFECT THE NUCLEASE-SENSITIVE SITE IN SIMIAN VIRUS 40 CHROMATIN.

Gerard RD, Woodworth-Gutai M, Scott WA
Dept. Biochemistry, Univ. Miami Sch. Medicine, Miami, FL, 33101
Mol Cell Biol; 2(7):782-788 1982

Nuclear extracts from in(Or)-1411-infected cells were incubated with MnCl2, allowing endogenous nuclease to cleave within the nuclease-sensitive regions. Introduction of deletions into a simian virus 40 (SV40) variant enabled a quantitative comparison between the nuclease sensitivity of the segment carrying the deletion and the unaltered copy elsewhere on the viral genome. Restriction enzyme analysis and heteroduplex mapping gave patterns identical to that of in(Or)-1411 DNA except for deletion of sequences within the inserted segment. Endonuclease which is endogenous to BSC-1 cell nuclei was used to cleave 32P-labeled chromatin to a limited extent. Variant in(Or)-1411 preferentially cut within each of the duplicate segments. Deletion mutant chromatin displayed nuclease sensitivity in segment I which is comparable to the parent. In(Or)-1411-dl12, -dl14, and -dl46 showed little or no preferential cleavage in region II. Mutants dl9, dl10, dl16, and dl42 retained the characteristic nuclease sensitivity in region II. Locations of the preferentially nuclease-sensitive regions were confirmed by restriction enzyme mapping of the linear DNA with KpnI. Specific cutting frequencies (corrected for a background assumed to be due to random cleavage) obtained for segments I and II in the mutants are presented. (29 Refs)

34. ISOLATION AND CHARACTERIZATION OF DEFECTIVE SIMIAN VIRUS 40 GENOMES WHICH COMPLEMENT FOR INFECTIVITY.

O'Neill FJ, Maryon EB, Carroll D
Dept. Cellular, Viral and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84148
J Virol; 43(1):18-25 1982

A new variant of simian virus 40 (EL SV40), containing the complete viral DNA separated into two molecules, was isolated. One DNA species contains nearly all of the early (E) SV40 sequences, and the other DNA contains nearly all of the late (L) viral sequences. Each genome was encircled by reiterated viral origins and termini and migrated in agarose gels as covalently closed supercoiled circles. EL SV40 or its progenitor appears to have been generated in human A172 glioblastoma cells, as defective interfering genomes during acute lytic infections, but was selected during the establishment of persistently infected (PI) green monkey cells (TC-7). PI TC-7/SV40 cells contained EL SV40 as the predominant SV40 species. EL SV40 propagated efficiently and rapidly in BSC-1, another line of green monkey cells, where it also formed plaques. EL SV40 stocks generated in BSC-1 cells were shown to be free of wild-type SV40 by a number of criteria. E and L SV40 genomes were also cloned in the bacterial plasmid pBR322. When transfected into BSC-1 cell monolayers, only the combination of E and L genomes produced a lytic infection, followed by the synthesis of EL SV40. However, transfection with E SV40 DNA alone did produce T-antigen, although at reduced frequency. (Author abstract) (28 Refs)

35. DISCRETE REGIONS OF SIMIAN VIRUS 40 LARGE T ANTIGEN ARE REQUIRED FOR NONSPECIFIC AND VIRAL ORIGIN-SPECIFIC DNA BINDING.

Prives C, Barnet B, Scheller A, Khoury G, Jay G
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
J Virol; 43(1):73-82 1982

The nondefective adenovirus Type 2 (Ad2)-simian virus 40 (SV40) hybrid viruses, Ad2+ND2 and Ad2+ND4, have been used to determine which regions of the SV40 genome coding for the large tumor (T) antigen are involved in specific and nonspecific DNA binding. Ad2+ND2 encodes 45,000 Mr (45K) and 56,000 Mr (56K) T antigen-related polypeptides. The 45K polypeptide did not bind to DNA, but the 56K polypeptide bound nonspecifically to calf thymus DNA. Ad2+ND4 encodes 60,000 Mr (60K), 66,000 Mr (66K), 70,000 Mr (70K), 74,000 Mr (74K), and 90,000 Mr (90K) T antigen-related polypeptides, all of which bound nonspecifically to calf thymus DNA. However, in more stringent assays, where tight binding to viral origin sequences was tested, only the 90K protein specified by Ad2+ND4 showed specific high affinity for sequences at the viral origin of replication. From these results and previously published experiments describing the SV40 DNA integrated into these hybrid viruses, it was concluded that SV40 early gene sequences located between 0.39 and 0.44 SV40 map units contribute to nonspecific DNA binding, whereas sequences located between 0.50 and 0.63 SV40 map units are necessary for specific binding to the viral origin of replication. (Author abstract) (41 Refs)

36. ISOLATION AND CHARACTERIZATION OF SIMIAN VIRUS 40 EARLY REGION DELETION MUTANTS.

Sompayrac LM, Danna KJ
Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO, 80309
J Virol; 43(1):328-331 1982

We constructed a tsB4/dl884 double-mutant helper virus and used it to isolate two simian virus 40 early region deletion mutants that lack about half of the DNA sequences normally used to encode the large tumor antigen (T). Both mutants make a normal-sized small t antigen, but neither mutant can replicate its DNA in the absence of a T+ helper. (Author abstract) (15 Refs)

37. MAPPING OF A DNA-BINDING DOMAIN OF SIMIAN VIRUS 40 T-ANTIGEN USING NON-DEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Montenarh M, Deppert W, Henning R
Dept. Biochemistry, Univ. Ulm, P.O. Box 4066, 7900 Ulm, W. Germany
FEBS Lett; 142(1):129-132 1982

In the attempt to localize a nonspecific DNA-binding region in the polypeptide chain of tumor antigen (T-Ag), a comparison was made between the calf thymus DNA-binding properties of simian virus 40 (SV40) T-Ag from SV40-transformed human cells and T-Ag related polypeptides coded for by Ad+ND2 and Ad2+ND4. The study suggests a DNA-binding domain inside the polypeptide chain of T-Ag located between maximally 0.53 and 0.39 SV40 DNA map units. (21 Refs)

38. MAPPING OF RESTRICTION FRAGMENTS AND TRANSFORMING ABILITY OF ADENOVIRUS 31.

Sawada Y, Yamashita T, Kanda F, Sekikawa K, Fujinaga K
Dept. Molecular Biology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Tumor Res (Sapporo); 16:7-17 1981

The cleavage maps of adenovirus 31 (Ad31) DNA with five restriction endonucleases and the localization of the transforming ability of the genome is reported. Specific fragments induced by restriction with EcoR1, BamH1, HindIII, SalI, and SmaI were identified via agarose gel electrophoresis. The fragments A and F of EcoR1 digests, the fragments B and E of BamH1 digests and the fragments C and G of HindIII digests were localized at the ends of the Ad31 genome. When the HindIII-C and G fragments were used to transfect subconfluent monolayers of 3Y1 cells, transformed foci became visible 3 wk later in the -G fragment-treated cultures. No transformation occurred in mock-transfected or -C fragment transfected cells. Thus the transforming ability of Ad31 is localized at the end of the genome where HindIII-G maps. (23 Refs)

39. IMPROVED INFECTIVITY OF REASSEMBLED POLYOMA VIRUS.

Yuen LK, Consigli RA
Div. Biology, Section Virology and Oncology, Kansas State Univ., Manhattan, KS, 66506
J Virol; 43(1):337-341 1982

Polyoma virus was dissociated into capsomeres (18, 12, and 5S) and a DNA-protein complex (48S) with Ca++ chelator, ethyleneglycol-bis- ethyleneglycol-bis-N,N'-tetraacetic acid, and the reducing agent, 2-mercaptoethanol. The reaction was maintained at pH 5.0. Reassembly of the dissociated components to complete virions was accomplished by dialyzing these components overnight at 4 C against the reassembly buffer containing CaCl2, dimethylsulfoxide, Triton X-100, and 0.01 M Tris-acetic acid (pH 5.0). Reconstituted particles ranged from 240S complete virions to lighter intermediate species. Approximately 25% of the dissociated particles could be physically reassembled to complete virions. These virions regained 12.5% of their hemagglutination ability and as much as 6.7% of their original infectivity. The infectivity of these reassembled particles represented a 100-fold increase in infectivity compared with that of the particles that were dissociated and reassembled at pH 7.4. Biochemical analysis showed that the polyoma viral receptor of the virions reassembled at pH 7.4 was greatly reduced, whereas virions reassembled at pH 5.0 retained their receptor. Reassembly could be further improved by additions of either exogenous capsomeres or DNA-protein complex to the reassembly reaction mixture. (Author abstract) (18 Refs)

IMMUNOLOGICAL STUDIES

40. ANTIGENS CROSS-REACTING WITH TUMOR VIRUS PROTEINS AS PROGNOSTIC MARKERS IN PATIENTS IN CHRONIC MYELOID LEUKEMIA (CML)-BLAST CRISIS (MEETING ABSTRACT).

Hehlmann R, Schetters H, Erfle V, Luz A, Pralle H
Universitat Munchen, Munchen, W. Germany
Onkologie; 4(5):254 1981

As part of the chronic myeloid leukemia (CML) blast crisis study of the SHG serum samples from 23 patients with CML blast crises were tested for antigens, antibodies, and immune complexes that cross react with coat glycoprotein gp70 of simian sarcomas virus SiSV. The presence of these structures was correlated with survival or treatment outcome. Approx half of the sera were positive for 1 or more of the structures cross-reacting with SiSV gp70, the other half was negative. Clinical information was available for 16 of the 23 patients. Of these 16 patients, those with cross-reacting antigens, antibodies or immune complexes (9 patients) had an av survival time after diagnosis of 2.5 mo whereas the patients without cross-reacting antigens (7 patients) had an av survival time of 7.4 mo. The difference in survival times between the 2 groups is significant (p less than 0.005, Fisher test). We conclude that the presence of antigens cross-recting with SiSV gp70 is associated with shorter survival time and this antigen has possible prognostic significance. (no Refs) (In GER)

41. CELL-MEDIATED IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS ANTIGENS BY PATIENTS WITH HYPERPLASTIC BENIGN BREAST DISEASE.

Cannon GB, Barsky SH, Alford TC, Jerome LF, Tinley V, McCoy JL, Dean JH
Immunotoxicology Section, Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, MD, 20795
JNCI; 68(6):935-943 1982

Peripheral blood leukocytes of patients with preoperative breast cancer, benign breast disease, and benign gynecologic disorders and normal healthy females were tested, as blind coded specimens, with murine mammary tumor virus (MuMTV) antigens in the direct and indirect leukocyte migration inhibition (LMI) assays. The incidence of reactivity by patients with breast cancer was low. (From 5 to 35% breast cancer patients reacted, depending on which group of control individuals they were compared to and what antigen was used.) Nonparametric analyses showed no differences between control groups (normal donors and patients with gynecologic disorders) and breast cancer patients with either assay. However, there was a significant difference between benign breast disease patients with hyperplasia and (1) benign breast disease patients without hyperplasia (p less than 0.03) and (2) patients with gynecologic disorders (p less than 0.040) in the direct assay when it was performed blindly with the gp52 antigen. Patients with hyperplasia (benign breast disease as well as breast cancer) had a higher incidence of enhanced migration in the indirect test than breast disease patients without hyperplasia. The enhanced migration to the MuMTV was correlated to enhanced migration to a 3-M KCl extract of the breast cancer cell line MCF-7 in simultaneous tests. Thus the LMI assays with MuMTV antigens do not appear valuable in breast cancer diagnosis, but they may help to identify a small group of benign breast disease patients whose breast pathology is thought to be associated with a high risk for developing breast cancer. (Author abstract) (20 Refs)

42. LYSIS OF AUTOLOGOUS EPSTEIN-BARR VIRUS-INFECTED B CELLS BY CYTOTOXIC T LYMPHOCYTES OF RHEUMATOID ARTHRITIS PATIENTS.

Tsoukas CD, Carson DA, Fong S, Slovin SF, Fox RI, Vaughan JH
Dept. Clinical Res., Scripps Clinic Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Clin Immunol Immunopathol; 24(1):8-14 1982

Since B lymphocytes of patients with rheumatoid arthritis (RA) have a higher rate of Epstein-Bar virus (EBV)-induced transformation than normal B cells, we have investigated whether this phenomenon is related to defective cytotoxic T-cell control of emerging B-cell clones. We have studied the in vitro generation of cytotoxic T lymphocytes specific for antigens appearing on autologous B cells after EBV infection using lymphocytes from six patients with RA. Cytotoxic cells were generated by two cycles of stimulation with mitomycin C-treated autologous B cells, and their lytic activity was assessed against 51Cr-labeled targets. As previously reported for lymphocytes of normal individuals, RA cytolytic T lymphocytes were induced only by EBV-infected B cells, not by noninfected B cells, and expression of the cytotoxicity required EBV-transformed targets. After primary in vitro stimulation with autologous EBV-infected B cells, the RA cytotoxic cells expressed higher lytic activity than the normal counterparts, but the difference was not statistically significant (p greater than 0.1). However, after secondary in vitro stimulation both groups displayed similar cytotoxic activities. In the presence of complement, monoclonal antibodies OKT8 (characterizing cytotoxic/ suppressor cells), SC1, and OKT3 (characterizing most T cells) reduced cytotoxicity by 80-90%; antibody OKT3 also reduced the lytic activity by 68% in the absence of complement. We conclude that the higher EBV-induced transformation rate seen with RA lymphocytes is not explained by a deficiency in this EBV-specific cytotoxic T cell. (Author abstract) (29 Refs)

43. SOLID-PHASE RADIOIMMUNOASSAYS FOR EPSTEIN-BARR VIRUS-ASSOCIATED ANTIGENS.

Dolken G, Gier A, Finke J, Weitzmann U
Abt. Hamatologie und Onkologie, Medizinische Universitatsklinik, Hugstetter Strasse 50, D-7800 Freiburg, W. Germany
Ric Clin Lab; 12(1):307-312 1982

Epstein-Barr virus (EBV)-associated antigens EA (early antigen), MA (membrane antigen) and VCA (viral capsid antigen) have been detected and defined by the reaction of human sera with selected targets cells. Solid-phase radioimmunoassays for the EBV-associated nuclear antigen (EBNA), EA, VCA and MA have been established by use of antigen containing cell extracts immobilized in polyacrylamide gel and 125I-labeled IgG prepared from anti-EBV positive and negative sera. Methods are given for the preparation of specific reagents for these antigens. (9 Refs)

44. SUPPRESSOR T CELLS ACTIVATED BY AUTOLOGOUS B-CELL DERIVED LINES INHIBIT BLASTOGENIC RESPONSES BY PERIPHERAL LYMPHOCYTES TO MITOGENS OR AUTOLOGOUS LYMPHOBLASTOID CELL LINES.

Tsukuda K, Tsukuda Y, Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
Cell Immunol; 69(2):291-304 1982

EBV-transformed B-cell lines (LCL) suppressed peripheral lymphocyte responses to mitogens (PHA, PWM, and protein A). Cell separation experiments have shown that LCL cells activate autologous radiosensitive suppressor T cells that inhibit T-cell responses to mitogens (PHA and Con A) and to the autologous lymphoblastoid cell line itself. The significance of this autologous response and the way it may reflect on the effect of the suppressor T cells on the regulation of potential autoimmune responses is considered in relation to the in vivo phenomena observed in the course of acute mononucleosis. (Author abstract) (37 Refs)

45. LEUKOCYTE MIGRATION INHIBITION INDUCED BY EPSTEIN-BARR VIRUS ANTIGENS. IMMUNITY IN INFECTIOUS MONONUCLEOSIS AND SOME IMMUNODEFICIENT AND IMMUNOSUPPRESSED STATES.

Szigeti R, Klein E, Masucci MG, Ernberg I, Svedmyr E, Klein G
II. Gyermekklinika, Semmelweis Orvostudomany Egyetem, Budapest, Hungary
Orv Hetil; 123(20):1217-1221 1982

Leukocyte migration inhibition (LMI) elicited by Epstein-Barr virus (EBV) antigens was studied in 13 patients with infectious mononucleosis (IM), 2 patients with chronic mononucleosis, 4 with sex-linked lymphoproliferative disease and in 12 patients with neoplastic diseases (5 with Hodgkin's disease, 6 with non-Hodgkin's lymphoma and 1 with chronic lymphocytic leukemia). Appreciable LMI was observed in the patients with IM in response to enriched early antigen-virus capsid antigen (EA/VCA) extracts. Similar LMI of mononucleosis type (sensitivity to EA/VCA and insensitivity to EBV nuclear antigen (NA)) was seen in chronic mononucleosis as well, while the patients with sex-linked lymphoproliferative disease failed to respond to any EBV antigens. Tumor patients with elevated EBV antibody titers either showed LMI similar to that seen in healthy, seropositive controls or LMI of the mononucleosis type. The findings suggest that an intact immune system is necessary for LMI to occur in response to EBVNA or to crude cellular extracts containing mainly EBVNA, while sensitivity to EA/VCA is present when the immune system is impaired to a certain extent. Late hypersensitivity reaction in vitro is absent in severe immunodeficiency or immunosuppression. (42 Refs) (In HUN)

46. EPSTEIN-BARR VIRUS ANTIGENS -- A CHALLENGE TO MODERN BIOCHEMISTRY.

Thorley-Lawson DA, Edson CM, Gellinger K

Dept. Medicine, Div. Geographic Medicine, Tufts Univ. Medical Sch., Boston, MA, 02111

Adv Cancer Res; 36:295-348 1982

The serologically defined antigens of Epstein-Barr virus (EBV) are reviewed, including transformation antigens, early antigens, and late antigens. EBV nuclear antigens; lymphocyte-determined membrane antigens; intracellular early antigens and early membrane antigens; late membrane antigens and viral capsid antigens; the molecular biology of antigens and the polypeptides; and immune responses to viral antigens are discussed. Of the 50 or more polypeptides that could theoretically be coded by the 85-90 x 10(6) mol wt of unique DNA in EBV, 20-25 polypeptides are known. Defining the specificity and function of EBV for various antigens will require use of a permissive in vitro system. Since this has not been discovered, the use of monoclonal reagents seems to be the most promising alternative. The use of the cottontop marmoset as an experimental subject for elucidating the role of neutralizing antibodies in preventing the establishment of infection may be defended in terms of the animal's lack of immune responsiveness. Its suitability for studies of infection establishment and the usefulness of studies of isolation of individual membrane antigen components, a goal which is currently not feasible, are discussed. Viral subunit vaccination in primates is the first step in understanding the the interaction of EBV with the immune response during infection, which may eventually lead to preventive measures in man. (212 Refs)

47. EPSTEIN-BARR VIRUS-ASSOCIATED EARLY ANTIGEN: DEVELOPMENT OF A SPECIFIC RADIOIMMUNOASSAY (MEETING ABSTRACT).

Dolken G, Bauer G, Lohr GW

Medizinische Universitatsklinik Freiburg, Freiburg, W. Germany

Onkologie; 4(5):260 1981

Epstein-Barr virus (EBV) is associated with 2 malignant human tumors: Burkitt's lymphoma and carcinoma of the nasopharynx. Serum antibody titers against EBV-associated early antigen (EA) appear to be of prognostic significance in these tumors. Since no quantitative methods are available to detect this antigen in EBV genome-bearing cells, we developed 2 different radioimmunometric test procedures which permit quantitative analysis of this antigen in various cell lines. Biochemical characterization of the antigen has begun. (no Refs) (In GER)

48. CHARACTERIZATION OF PERIPHERAL LYMPHOID CELLS (DOWNEY CELLS) DURING INFECTIOUS MONONUCLEOSIS (IM), USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Fjelde A, Ozer H, Kellam J, Bennett P
Roswell Park Memorial Institute, Buffalo, NY, 14263
In Vitro; 18(3,part2):309 1982

The present study is part of a project concerning the relationship of IM and human lymphoma-leukemia, in which we have reported the presence of Paul-Bunnell (PB) antigen, the antibody which is present in high titer and diagnostic for IM. The present study is an investigation of the nature of the peripheral blood cell population in terms of surface antigens, using monoclonal antibodies and the cell sorter. A preliminary study using other methods showed an absolute increase in T lymphocytes. During early (1st week) IM, we found that a high percentage of responders to monoclonal antibodies repesented T cells, suppressor-cytotoxic (SC) cells and E rosette responding cells. At 1 month peripheral T cells (OKT-3) remained high, but all other values returned to normal or below. Response to OKT-4 antibodies representing helper-inducer T cells (H), was low at both periods. Values for OKT-6, 8, 11a OKIa and OKM1 were above normal at 1 week, but returned to normal at 1 month. The H/SC ratio was less than 1 at both periods, demonstrating an inversion of the normal values. Induction of IM by EM virus infection of B lymphocytes causes T cell reactive Downey cell proliferation, apparently representing a control system. (no Refs)

49. VIROLOGIC AND IMMUNOHISTOCHEMICAL STUDIES OF CARCINOMA OF THE NASOPHARYNX (MEETING ABSTRACT).

Wilmes E, Meister P, Nathrath W, Wolf H
No affiliation given
Experimentelle Tumorforschung in der Hals-Nasen-Ohrenheilkunde, February 25-27, 1982, Dusseldorf, W Germany Universitat Dusseldorf; 1982

According to the World Health Organization's Tumor Classification the term 'lymphoepithelial carcinoma' is no longer justifiable because it is treated therein as just undifferentiated squamous epithelial carcinoma in the same way as 'syncytial carcinoma' or 'transitional epithelial carcinoma.' Based on our current study series of approx 70 patients with carcinoma of the nasopharynx we examined the manner in which various histological types of carcinoma are related to different serologic findings. The results showed that antibody titers in uncornified and undifferentiated carcinomas with no lymphocyte participation were far less than in lymphoepithelial carcinoma. Using immunohistochemical techniques an attempt was made to demonstrate the immunomorphologic correlate of these virus-associated serologic findings in formol-fixed and paraffin-embedded tissue samples. The results are compared with the controls and the findings discussed. (no Refs) (In GER)

50. PRODUCTION OF HEPATITIS B E ANTIBODY IN EPSTEIN-BARR VIRUS-INDUCED B LYMPHOCYTE CELL LINES.

Furuya Y, Inoue M, Yoshida Y, Yoshihara N, Takada M
Kanagawa Prefectural Public Health Lab., 52-2 Nakao-cho, Asahi-ku, Yokohama 241, Japan
J Med Virol; 9(4):293-297 1982

A specific antibody-producing lymphocyte cell line (LCL) was established from peripheral blood lymphocytes of a donor carrying hepatitis B e (HBe) antibody (anti-HBe). Cultures were depleted of T-cells by removal of erythrocyte-rosetting cells, and were subsequently infected in vitro with Epstein-Barr virus. Upon initial establishment of the LCL anti-HBe could not be detected by solid-phase radioimmunoassay (RIA), double immunodiffusion, or reverse passive hemagglutination inhibition (R-PHI). However, after centrifugal harvesting of cells rosetting with HBe antigen-coupled sheep red blood cells the 10-fold concentrated supernatant showed the presence of anti-HBe by all three methods after 1 wk. The anti-HBe titer was 64-fold at 1 wk, 256-fold at 2 wk, 128-fold at 3 wk, but undetectable at 5 wk using R-PHI. RIA could not detect anti-HBe after 5 wk either. Anti-HBe activity in the culture supernatant was not destroyed by treatment with 0.2 M 2-mercaptoethanol at 2 wk, indicating that the antibody was not sensitive to this agent. and that the anti-HBe was IgG. The decline in anti-HBe activity in long-term cultures was not associated with any change in growth pattern. (12 Refs)

51. PREVALENCE OF ANTIBODIES AGAINST HERPES SIMPLEX AND ADENOVIRUS IN ORAL AND CERVICAL CANCER PATIENTS - A PRELIMINARY REPORT.

Kumari TV, Shanmugam J, Prabha B, Vasudevan DM
Research Division, Regional Cancer Centre, Trivandrum 695011, India
Indian J Med Res; 75:590-592 1982

A total of 277 serum samples from oral cancer patients (111), cervical cancer patients (66), and healthy controls (100) were investigated for the presence of antibodies against herpes simplex virus (HSV) and adenoviruses by means of micro-complement fixation test (CFT). HSV antibodies were found in 56.5% of oral cancer patients, 69% of cervical cancer patients and 38.4% of healthy controls. The present study indicates the high prevalence of HSV antibodies in oral and cervical cancer patients and failed to reveal any correlation between adenoviruses and human cancer. (Author abstract) (10 Refs)

52. NATURAL KILLER CELLS (NK) IN RESISTANCE TO LEUKEMIA AND VIRUSES IN BONE MARROW TRANSPLANT (BMT) RECIPIENTS (MEETING ABSTRACT).

Ching C, Lau W, Wong L, Paik Y, Jim R, Wilkinson R, Miller C, Loh K, Seto D, Yoshitsugi H, Ching N
University of Hawaii-Cancer Center of Hawaii, Honolulu, HI, 96813
Proc Am Assoc Cancer Res; 23:1063 1982

In BMT recipients, normal pre-tranplant NK(HSV-1), a herpesvirus injected fibroblast target, has correlated with the subsequent development of graft-versus-host disease (GVHD). Reports by others, of NK(K562), a leukemia cell, appear to differ. Thus, NK(K562), NK(HSV-1) and to normal fibroblast, NK(FS) were examined in 12 patients with hematopoietic malignancies. NK function was deficient in all 7 patients with acute leukemia in relapse, 3 with aplastic anemia (AA), normal in 2 in remission. Human leukocyte interferon (IFNalpha) in vitro augmented NK in 2 AA, and acute myelocytic leukemia (AML) in remission, and not in patients in relapse. Six patients received BMT from an HLA identical sibling. Five patients who developed GVHD had low pre-transplant NK or NK cells inducible by IFNalpha, except for one in complete remission. NK post-BMT was normal with one exception. In an AML patient with severe GVHD, NK cells killed non-specifically both fibroblast targets: NK(FS) 15%, NK(HSV-1) 31%. NK was normal in patients surviving viral infections. CMV-interstitial pneumonitis was fatal in 1 patient with low NK(HSV-1) 6%, NK(FS) 1%, NK(K562) 20%. His lymphocytes treated with IFN alpha did not increase NK(HSV-1), NK(FS); NK(K562) increased from 20% to 33%. This patient had 1% large granular lymphocytes (LGL). These studies support a biological role for NK function in resistance to leukemia and viral infections in immunodeficient patients. (no Refs)

53. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR-ASSOCIATED ANTIGENS.

Starling JJ, Sieg SM, Beckett ML, Schellhammer PF, Ladaga LE, Wright GL
Dept. Biochemistry, Eastern Virginia Medical Sch., Norfolk, VA, 23501
Cancer Res; 42(8):3084-3089 1982

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of P3X63/Ag8 mouse myeloma cells with spleen cells from BALB/c mice immunized against the prostate cancer cell line DU145. The hybrids were screened for antibody production using glutaraldehyde-fixed cells in a solid-phase radioimmunoassay. Antibody-binding specificity was also checked by quantitative adsorption, membrane immunofluorescence, and complement-dependent cytotoxicity assays. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to several prostate and bladder cancer cell lines but did not bind to a variety of other normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Quantitative adsorption studies demonstrated that the 83.21 monoclonal antibody was strongly reactive to membrane preparations from human prostate adenocarcinoma tissue and a liver metastasis of prostate carcinoma. Little or no binding activity was observed against two other prostate carcinomas, benign prostatic hyperplasia, normal prostate, or normal liver. Binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human leukocyte antigen, Beta2-microglobulin, HLA-Dr antigens, fibronectin, or prostate antigen. The data indicate that we have isolated a monoclonal antibody that binds to an antigen(s) expressed by several urogenital carcinoma cell lines as well as human prostate tumor tissue and that the antibody is not directed against well-known human tumor cell markers. (Author abstract) (37 Refs)

54. CYTOTOXIC T CELLS IN CYTOMEGALOVIRUS INFECTION. HLA-RESTRICTED T-LYMPHOCYTE AND NON-T-LYMPHOCYTE CYTOTOXIC RESPONSES CORRELATE WITH RECOVERY FROM CYTOMEGALOVIRUS INFECTION IN BONE-MARROW-TRANSPLANT RECIPIENTS.

Quinnan GV, Kirmani N, Rook AH, Manischewitz JF, Jackson L, Moreschi G, Santos GW, Saral R, Burns WH
Div. Virology, Office Biologics, Bureau Drugs and Biologics, Food and Drug Admin., 8800 Rockville Pike, Bethesda, MD, 20205
N Engl J Med; 307(1):7-13 1982

Prospective studies were conducted of cell-mediated cytotoxic response in 58 recipients of syngeneic or allogeneic bone-marrow grafts. Emphasis was placed on the period 4-12 wk after transplantation, when the risk of cytomegalovirus (CMV) infection is greatest. Forty-three patients had CMV during the period of study; 23 patients survived infection. CMV infection was the principal cause of death in 12 patients, and an additional 8 patients died from other causes during acute CMV infection. A significant rise in cytotoxicity was observed early in the course of infection, as measured by CMV-specific cytotoxic lymphocyte response. Evidence of CMV-specific cytotoxic response was found in all patients who survived infection. Patients with nonfatal infections showed significantly greater response than those with fatal infections. The natural-killer-cell activity of lymphocytes from patients with nonfatal infections was within the normal range both before and after the onset of infection, but in the group with fatal infection, lower than normal activity was observed in 4 patients before the onset of infection and in 11 patients afterward. Neither the presence nor level of complement-fixing antibodies in donors or recipients before transplantation correlated with the risk of infection or the likelihood of recovery. The finding that the capacity for cytotoxic response, mediated both by HLA-restricted T lymphocytes and nonrestricted non-T lymphocytes during CMV infection, correlated with recovery strongly suggests that these effector cells mediate recovery from CMV infection. (32 Refs)

55. NK ACTIVITY AND ITS RADIORESISTANCE IN LEUKEMIA AND BONE MARROW TRANSPLANTATION (MEETING ABSTRACT).

Schacter B, Brovall C, Polmar S, Pierce G, Coccia P
Case Western Reserve University, Cleveland, OH
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Natural killer (NK) activity may play a role in immune modulation, GVHD (graft verus host disease) and in viral infections. We have evaluated NK activity, and its resistance to gamma irradiation in leukemic patients in remission under evaluation for bone marrow transplantation (BMT) and following engraftment of HLA identical bone marrow. NK activity of peripheral blood mononuclear cells (PBMNC) of 11 patients with acute leukemia was slightly lower than 11 control subjects (x +/- SEM patients: 18.2% +/-4.2%, controls: 27.0% +/-4.1%, p equals .08). Radioresistance of NK activity is controlled by an X linked gene. Ten of eleven patients were radiosensitive by genotyping. Residual NK activity (RA) after 3000 rads of 10 sensitive control subjects was 13.8% +/-1.9% of unirradiated activity; in 10 leukemia patients RA equals 41.7% +/-8.1% (p equals .003) suggesting recruitment of a cell expressing radioresistant NK activity in the leukemics in remission. NK activity and its radiosensitivity was evaluated post-BMT in 9 patients: 7 leukemics, a child with Ewing's sarcoma and a child with SCID (severe combined immunodeficiency disease). The SCID patient, who received without ablation an HLA-A, B, C, D matched buffy coated infusion from a maternal grandfather, showed lymphoid engraftment documented by improved immunological function, marrow and blood karyotype and mild liver GVHD. Conversion of the granulocyte genetic markers did not occur. Conversion of NK radioresistance phenotype did occur. Conversion of NK radioresistance phenotype occurred in 1/2 discordant leukemic recipient/donor pairs. NK activity and radioresistance in the immediate post-transplant period was evaluated with regard to GVHD and viral infection. In 10 assays of 6 patients, engrafted with sensitive donors, RA of greater than 30% after 3000 rads was positively associated with documented Varicella-Zoster virus (VZV) infection (py less than .025) and not associated with GVHD. NK activity of lymphocytes stimulated in vitro is radioresistant. These data are consistent with the non-myeloid, bone marrow origin of spontaneous NK activity and the recruitment of other cells expressing radioresistant NK activity in leukemia and in VZV infection post-BMT. (no Refs)

VIRAL STUDIES IN HUMAN CANCER

56. ASSOCIATION OF HLA-DR5 WITH MYCOSIS FUNGOIDES AND KAPOSI'S SARCOMA (MEETING ABSTRACT).

Pollack MS, Safai B, Myskowski PL, Dupont B
Sloan-Kettering Institute for Cancer Research, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Mycosis Fungoides (MF) is a cutaneous T-cell lymphoma while Kaposi's sarcoma (KS) is a multicentric neoplasm which often has its primary manifestation in the skin. An outbreak of KS in young homosexual men has recently been observed in New York City and California which differs from the 'classic' North American disease in younger age of onset and clinical presentation. Although the exact mechanism for initiation of either disease is still unknown, a viral mechanism has been suggested in both cases. Specifically, retroviruses have been associated with some tumor cell lines of MF, and cytomegalovirus has been associated with KS. In order to investigate the possible role of HLA-associated variations in genetic susceptibility, 64 patients with histologically documented MF and 32 patients with histologically documented KS were typed for HLA-A,B,C antigens. Most of these patients were also typed for HLA-DR antigens. A significant increase in DR5 was the only statistically significant deviation in HLA antigen frequencies in either group (50% in MF and 60% in KS in comparison with 20% in controls). The increase in DR5 was especially striking in the subgroup of KS patients with the particularly aggressive form of KS found in the young homosexual males but the increase was statistically significant in both groups. HLA-DR5 has also been associated with scleroderma and juvenile rheumatoid arthritis. Immunologic alterations are involved in the pathogenesis of both, but viral infection may also be a factor. It is also interesting to note that an association of DR5 with another malignant disease, renal cell carcinoma, has also been reported. The associations of MF and KS with DR5 thus suggest that some individuals with the DR5 antigen may be at higher genetic risk for virally initiated and/or neoplastic diseases, possibly through an HLA-linked defect in the immune system. (no Refs)

57. THE HLA SYSTEM IN PATIENTS WITH KAPOSI SARCOMA (MEETING ABSTRACT).

Walker M, Rubinstein P, Carrier C, Carpenter C, Kressner J, Friedman-Kien A
The Lindsley F. Kimball Research Institute, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Classical Kaposi Sarcoma (KS) is an infrequent malignancy with characteristically slow and indolent progress in Causcasians. It affects mostly elderly Jewish and Italian males. Cytomegalovirus has been recovered from KS cells of African patients. Recently, an epidemic of KS has been declared affecting male homosexuals in the USA among whom it is much more malignant. We report here on a sample of 30 young homosexual males from New York City studied for 16 HLA-A, 27 HLA-B, 7 HLA-C and 10 HLA-DR antigens. A group of 13 patients with the classical form of KS were similarly typed. A 'control' sample of 26 patients with polyadenopathy but without KS from the homosexual community in New York is also included. All these individuals have been additionally studied for responsiveness to mitogens and allogeneic lymphocytes, for skin reactivity in delayed hypersensitivity and for the serum levels of immunoglobulins and immune complexes. The three samples differ only in the frequency of antigen DR5: 60% in the 'young KS' and 62% in the 'classical KS' vs 23% in the 'controls'. The two samples of KS patients do not differ from each other in HLA frequencies; the 'controls' do not differ from the frequencies found in 231 'normal' New York Caucasians. The X2 for the differences in the frequency of DR5 between all 43 KS patients (61%) and the 231 'normals' (23.4%) is 24.12. This difference is significant after correction for 60 antigens. These results suggest the existence of HLA-associated genetic susceptibility to KS that may be triggered by environmental factors which determine, also the clinical aspects and degree of malignacny of the disease. (no Refs)

58. THE EPIDEMIC OF ACQUIRED IMMUNE DYSFUNCTION IN HOMOSEXUAL MEN AND ITS SEQUELAE. OPPORTUNISTIC INFECTIONS, KAPOSI'S SARCOMA, AND OTHER MALIGNANCIES: AN UPDATE AND INTERPRETATION.

Levine AS
Div. Cancer Treatment, NCI, Building 31, Room 3A49, Bethesda, MD, 20205
Cancer Treat Rep; 66(6):1391-1395 1982

Incidence of pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma (KS), survival, risk factors, immune dysfunction, genetics, course of the illness, and treatment are reviewed. Three-hundred patients (290 men) with a new syndrome have been reported; 135 had CP, 115 KS, 28 both diseases, and 22 other opportunistic infections. The mortality rate has been 40%; however, greater than 70% of patients with earliest diagnosed cases have died. Eighty-five percent of the 300 patients have been less than 45 yr old, with a median of 35 yr. Of the 290 men, 242 have been homosexual or bisexual. Ninety-eight percent of the homosexual male patients have had a history of exposure to nitrites, mainly amyl or butyl inhalants, but no one nitrite preparation is over-reported, suggesting that whatever the involvement of nitrites in the syndrome is not due to a contaminant. A very extensive case-control study will be required to sort out the relative contributions of nitrites and transmissible microbes; independent risk factors may be impossible to be identified. The breadth of immune defects observed in the syndrome explains the broad gap in host defenses against all classes of microbes that are associated with cellular immunity. The possibility exists that once the patients have become immunodeficient, a considerable reactivation of the cytomegalovirus infection occurs. As many as one third of KS patients in the epidemic appear to be developing other malignancies, as occurs with other KS patients, including the sporadic and endemic patients and the patients in renal transplant recipients or in patients receiving chronic immunosuppressive therapy. (17 Refs)

59. DISSEMINATED KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Friedman-Kien AE, Laubenstein LJ, Rubinstein P, Buimovici-Klein E, Marmor M, Stahl R, Spigland I, Kim KS, Zolla-Pazner S
New York Univ. Medical Center, 530 First Ave., New York, NY, 10016
Ann Intern Med; 96(6,part1):693-700 1982

Nineteen cases from an epidemic of disseminated Kaposi's sarcoma in homosexual men were studied by clinical, virologic, immunologic, and genetic methods. The patients were all male homosexuals ranging in age from 29 to 52 yr, with histories of multiple sexually transmitted diseases and exposure to both prescription and recreational drugs. Sites of disease included skin (16 of 19 patients), lymph nodes (13 patients), gastrointestinal tract (12 patients), spleen (3 patients), and lung (1 patient). Most patients had elevated levels of serum immunoglobins, positive antibody titers to hepatitis A and B virus, cytomegalovirus and Epstein-Barr virus, and impairment of cell-mediated immunologic reactions. The frequency of HLA-DR5 in these patients was significantly elevated. Two of the 19 patients died. Although the precise cause of this epidemic is unknown, it is likely that a genetic predisposition, an acquired immunoregulatory defect, and one or more infectious agents and drugs may be involved. (Author abstract) (48 Refs)

60. WORKSHOP ON KAPOSI'S SARCOMA: MEETING REPORT.

DeWys WD, Curran J, Henle W, Johnson G
Clinical Investigation Branch, NCI, Landow Building, Room 4A04, Bethesda, MD, 20205
Cancer Treat Rep; 66(6):1387-1390 1982

Occurrence, epidemiology, virology-etiology, and treatment of Kaposi's sarcoma (KS) are reviewed. A clustering of cases of KS in homosexual men (HM) in New York City and California was reported; 55 patients with KS, 49 with Pneumocystis carinii pneumonia (PCP), and 11 with both diseases, either concurrently or sequentially. All patients were men, 94% of whom were homosexual or bisexual. Eighty percent of these patients were between 25-45 yr old. A national case/control study of KS and/or PCP among HM will be conducted by Centers for Disease Control, and laboratory studies coordinated with the study would be desirable. Of primary importance is the collection of appropriate, well-characterized specimens from KS patients and controls in a coordinated manner. Aliquots of specimens would be tested in several laboratories by possibly different techniques permitting comparison and correlation of results. The specimens to be collected include biopsy material (frozen or fresh) and sera. The virus-specific antibody spectrum and titers should be determined for patients with primary or recurrent cytomegalovirus infections, healthy or immunologically compromised carriers of the virus, and KS patients at various stages of the disease. Careful evaluation of the immune reactivities of KS prior to therapy and continuing thereafter is considered essential. In addition to identifying various types of leukocytes by monoclonal antibodies, their functional state must also be ascertained. A general format for any prospective study was proposed. Components of the protocol would include eligiblity, pathology confirmation, staging, immunologic evaluation, infection prophylaxis, and treatment. Treatment assignment should be based on the patient's clinical stage of disease as defined. Possible regimens are based on cumulative experience with KS and pilot studies currently in progress. (4 Refs)

61. AN OUTBREAK OF PNEUMOCYSTIS CARINII PNEUMONIA IN HOMOSEXUAL MEN.

Follansbee SE, Busch DF, Wofsy CB, Coleman DL, Gullet J, Aurigemma GP, Ross T, Hadley WK, Drew WL
Dept. Medicine, Univ. California, San Francisco, CA, 94143
Ann Intern Med; 96(6,part1):705-713 1982

Pneumocystis carinii pneumonia has rarely been reported in previously healthy persons over the age of 6 mo. Five cases of P carinii pneumonia in adult homosexual men, confirmed by biopsy results, are reported. All five patients were seropositive when tested for antibodies to cytomegalovirus and four had evidence of active concurrent cytomegalovirus infections. Kaposi's sarcoma was shown in two of the patients and one had possible Pneumocystis infection of the central nervous system as well as P carinii pneumonia. Three patients had second episodes of Pneumocystis pneumonia. Four of the five patients have died. Past or concurrent cytomegalovirus infection and homosexuality were the only common epidemiologic features in all five patients. (Author abstract) (57 Refs)

62. GASTROINTESTINAL INVOLVEMENT IN KAPOSI'S SARCOMA (MEETING ABSTRACT).

Saltz RK, Kurtz RC, Lightdale CJ, Safai B, Myskowski P, Urmacher C
Department of Medicine and Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Gastroenterology; 82(5,part2):1168 1982

Since September, 1981, we have evaluated ten male homosexual patients with biopsy-proven skin lesions of Kaposi's sarcoma. Nine are white, one is black, and their ages range from 32-50 (mean 40). We report the findings of upper gastrointestinal (UGI) endoscopy (8/10) and colonoscopy (7/10) in these patients. The typical appearing blue-red, raised, nodular Kaposi's lesions were identified in the stomach (4) and duodenum (2) in 5 of 8 patients. Biopsies were not initially positive because they were too superficial. Colonoscopy revealed normal findings in 4 patients, non-specific left-sided inflammatory changes in 2, and 1 patient had typical lesions of Kaposi's sarcoma in the sigmoid colon which were confirmed histologically. Three other patients with Kaposi's sarcoma have been seen. Autopsy done in two revealed diffuse GI involvement including the esophagus, stomach, small and large intestine, liver, spleen, and pancreas. We correlated the degree of skin involvement with the presence and location of the GI tract involvement. Eighty percent of those patients with advanced cutaneous disease had GI lesions. All of the patients with oral mucosal lesions had GI lesions. In one patient, treated with Interferon, in whom improvement of cutaneous lesions was seen, the UGI lesions also showed significant improvement. Seven of ten patients had blood type O+ which is twice the expected distribution of this blood type. Viral and immunologic studies are underway to further characterize this problem and attempt to identify etiologic agents. (no Refs)

63. EPSTEIN-BARR VIRUS-INDUCED DISEASES IN BOYS WITH THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP). UPDATE ON STUDIES OF THE REGISTRY.

Purtilo DT, Sakamoto K, Barnabei V, Seeley J, Bechtold T, Rogers G, Yetz J, Harada S, XLP Collaborators
Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Am J Med; 73(1):49-56 1982

Analyses of 100 subjects with the X-lined lymphoproliferative syndrome (XLP) in 25 kindreds revealed four major interrelated phenotypes: infectious mononucleosis, malignant B-cell lymphoma, aplastic anemia, and hypogammaglobulinemia. Eighty-one of the patients died. Two male subjects were asymptomatic but showed immunodeficiency to Epstein-Barr virus (EBV). Seventy-five subjects had the infectious mononucleosis phenotype and concurrently, 17 subjects of this group had aplastic anemia. All subjects with aplastic anemia died within a wk. Aplastic anemia did not accompany hypogammaglobulinemia or malignant lymphoma phenotypes. Hypogammaglobulinemia had been detected before infectious mononucleosis in there subjects, after infectious mononucleosis in five subjects, and was not associated with infectious mononucleosis in 11 boys with hypogammaglobulinemia. In nine subjects infectious mononucleosis appeared to have evolved into malignant lymphoma; however, the majority of patients with malignant lymphoma showed no obvious antecedent infectious mononucleosis. One subject had infectious mononucleosis following recurrent malignant lymphoma. Twenty-six of 35 lymphomas were in the terminal ileum. Results of immunologic and virologic studies of 15 survivors revealed combined variable immunodeficiency and deficient antibody responses to EBV-specific antigens. Mothers of boys with XLP exhibited abnormally elevated titers of antibodies to EBV. Subjects of both sexes with phenotypes of XLP should be investigated for immunodeficiency to EBV. Persons with inherited or acquired immunodeficiency may be vulnerable to life-threatening EBV-induced diseases. (Author abstract) (26 Refs)

64. MALIGNANT LYMPHOPROLIFERATIVE DISEASES INDUCED BY EPSTEIN-BARR VIRUS IN IMMUNODEFICIENT PATIENTS, INCLUDING X-LINKED, CYTOGENETIC, AND FAMILIAL SYNDROMES.

Purtilo DT
Dept. Pathology, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Genet Cytogenet; 4(3):251-268 1981

An attempt is made to develope an etiologic basis for malignant lymphoproliferative disorders (LPD). Topics reviewed include infectious mononucleosis and normal immune responses; immune deficiency predisposing to fatal lymphoproliferation; X-linked LPD predisposing to fatal infectious mononucleosis and malignant lymphomas; Epstein-Barr virus-induced LPD in renal transplant recipients; ataxia telangiectasia and its relationship to immune deficiency, increased chromosomal breakage, and lymphoproliferative malignancies; familial lymphoproliferative malignancies; male predominance of lymphoproliferative malignancies; cytogenetic errors and determination of phenotypes of lymphoproliferative malignancies; masquerading malignant histiocytosis syndrome; Epstein-Barr virus and familial immunodeficiency in Hodgkin's disease; epidemiology of Hodgkin's disease; Hodgkin's disease following infectious mononucleosis; the ability of immune deficiency to virus to induce Hodgkin's disease; the relationship of immunoregulatory defects to the production of immune deficiency, autoimmunity, or malignant lymphoma; and prelymphoma syndrome. (55 Refs)

65. INFECTIOUS MONONUCLEOSIS IN AN ADULT PROGRESSING TO FATAL IMMUNOBLASTIC LYMPHOMA.

Snydman DR, Rudders RA, Daoust P, Sullivan JL, Evans AS
New England Medical Center, Box 238, 171 Harrison Ave., Boston, MA, 02111
Ann Intern Med; 96(6,part1):737-742 1982

We report a case of infectious mononucleosis progressing to fatal immunoblastic lymphoma. The patient, a 44-yr-old man who may have had an immunoregulatory defect, failed to have an appropriate T-cell response to his Epstein-Barr (EB) viral infection. His active EB viral infection was manifest by seroconversion of IgM-viral capsid antibody and a greater than four fold rise in IgG-viral capsid antibody. Also, he transmitted his EB viral infection to his wife who became ill 1 mo after his death. Clinically the patient's illness was characterized by waxing and waning lymphadenopathy, persistent fever, diarrhea (similar to that associated with cholera), a coagulopathy, and gastrointestinal bleeding. The patient had pathologic findings of a diffuse immunoblastic lymphoma involving lymph nodes, small bowel, liver, pancreas, kidneys, lungs, and bone marrow. Immunologic cell markers showed the tumor to be polyclonal. (Author abstract) (23 Refs)

66. BURKITT'S LYMPHOMA.

Ziegler JL
Veterans Admin. Medical Center, San Francisco, CA
CA; 32(3):144-161 1982

Etiology, clinical features, staging, treatment, and immunology of Burkitt's lymphoma are reviewed. Most, but not all cases are associated with Epstein-Barr virus (EBV); the causative role of EBV, if it exists, may be related to differences in viral strains. In addition to EBV, genetic factors, immunoregulatory determinants related to environment, and possibly an RNA virus have also been suggested as causes. Systemic chemotherapy is the treatment of choice. After complete remissions lasting about 1 yr, recurrence is rare. Prognosis is directly related to the tumor burden upon initial presentation. Burkitt's lymphoma is one of a dozen neoplasms that can be cured by drugs alone. It is the most likely candidate for a virus-induced human tumor. Studies of the association of Burkitt's lymphoma and EBV led to the discovery of EBV as the cause of infectious mononucleosis. Experimental and clinical studies of Burkitt's lymphoma have led to important advances in immunobiology and tumor immunology. Promising approaches in immunotherapy include rapid removal of antigen excess and immune complexes from the circulation and enhancement of normal immunoregulatory controls of the body. (121 Refs)

67. HERPESVIRUS-SPECIFIC RNA AND PROTEIN IN CARCINOMA OF THE UTERINE CERVIX.

McDougall JK, Crum CP, Fenoglio CM, Goldstein LC, Galloway DA
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Proc Natl Acad Sci USA; 79(12):3853-3857 1982

Cloned probes of herpes simplex virus type 2 DNA were used in cytological hybridization experiments to detect herpesvirus RNA transcripts in the neoplastic cells of tumors of the uterine cervix. Virus-specific RNA was shown to represent transcription of limited regions of the genome, of which one is known to code for a DNA-binding protein that can be found by immunoperoxidase staining in the neoplastic cells of these tumors and has also been detected in cells transformed in vitro by this virus. (Author abstract) (56 Refs)

68. HEPATITIS B VIRUS AND PRIMARY HEPATOCELLULAR CARCINOMA: FAMILY STUDIES IN KOREA.

Hann HW, Kim CY, London WT, Whitford P, Blumberg BS
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Int J Cancer; 30(1):47-51 1982

Chronic infection with hepatitis B virus (HBV) is closely associated with the etio-pathogenesis of primary hepatocellular carcinoma (PHC). It has been proposed that infection with HBV early in life, frequently transmitted by an HBV-carrier mother, leads to persistent infection with HBV, which in turn is associated with the development of chronic active hepatitis (CAH), post-necrotic cirrhosis and PHC. If this view is correct, then there should be clustering of chronic carriers of HBV in families of patients with chronic liver disease. We tested this hypothesis in Korea by collecting serum from 132 patients with these chronic liver diseases admitted to the Seoul National University Hospital and 664 of their first-degree relatives. Sera were assayed for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs) and antibody to hepatitis B core antigen (anti-HBc). Almost all cases showed evidence of present or past infection with HBV. Mothers of patients were more frequently HBsAg(+) than age-matched women in the control population or wives of patients. Five of 23 fathers were also HBsAg(+) compared with 1 of 25 age-matched controls. There was a deficit of anti-HBs in the fathers of cases compared with the controls. Siblings of patients were frequently HBsAg(+), with the highest prevalence in brothers. Family history shows that five fathers, two mothers and five brothers of cases have died of PHC. These data are compatible with the hypothesis tested and lend further support to the view that prevention of infection with HBV will lead to a marked decrease in the incidence of CAH, cirrhosis and PHC in areas where these diseases are endemic. Members of the families of patients with these diseases are at high risk of developing persistent infection with HBV and chronic liver disease. It would be appropriate to focus preventive strategies on infants and children in such families. (19 Refs)

69. GENITAL WARTS AND CERVICAL CANCER. I. EVIDENCE OF AN ASSOCIATION BETWEEN SUBCLINICAL PAPILLOMAVIRUS INFECTION AND CERVICAL MALIGNANCY.

Reid R, Stanhope CR, Herschman BR, Booth E, Phibbs GD, Smith JP
Dept. Obstetrics and Gynecology, Sinai Hosp. Detroit, 6767 West Outer Drive, Detroit, MI, 48235
Cancer; 50(2):377-387 1982

A blind comparative survey was undertaken to study the prevalence of subclinical papillomavirus infection (SPI) in a representative sample of women treated surgically for invasive or preinvasive cervical neoplasia. According to a semiobjective rating system, 73 of 80 women (91%) with cervical neoplasia and 10 of 80 matched controls (12.5%) showed histological evidence of human papillomavirus (HPV) infection. Sixty of the controls (75%), but none of the study group, had normal cervicovaginal epithelium. A highly significant statistical relationship exists between subclinical papillomavirus infection of the lower genital tract and the occurrence of cervical neoplasia (F = 378; p less than 0.001; x2 = 109, p less than 0.001). The prevalence of SPI was 7x greater in the study group than in comparable controls of equivalent disease status. Because both are covariables of promiscuity, statistical associations exist between cervical neoplasia and all sexually transmitted diseases. However, the strength, specificity and consistency of this relationship suggest that SPI may be a precursor of cervical malignancy. This contention is given biologic plausibility by a broad fabric of supporting epidemiologic, virologic and clinocopathologic evidence. (Author abstract) (58 Refs)

70. CYTOLOGICAL AND CYTOGENETICAL STUDIES ON HUMAN MENINGIOMA.

Zang KD
Inst. Human Genetics, Univ. Saar, 6650 Homburg, W. Germany
Cancer Genet Cytogenet; 6(3):249-274 1982

Characteristics of meningiomas which make them a model system for the study of human cancer development are described. Meningiomas show a remarkably good correlation between karyotype and histological and growth patterns which particle cultures of the individual tumors develop in vitro. Histological classification of meningiomas is described. In contrast to true brain tumors, meningiomas occur most offten in the fifth and sixth decade of the life and occur twice as frequently in females as in males. Characterization of meningiomas according to their respective karyotype shows a highly significant shift in sex distribution. In tumors with normal karyotypes, the male:female sex ratio is 1:3 while in more aberrant forms the ratio is approx 1:1. Chromosomal indications for virus involvement in the etiology of meningiomas are presented along with immunofluorescence data, induction of virus particles, and demonstration of episomal Simian virus 40 (SV40) DNA in meningiomas. Experimental transformation of meningioma cell cultures and fibroblast cultures of the same patients with SV40 is described. (62 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

71. CHRONIC MYELOCYTIC LEUKEMIA (CML)-NEW DIAGNOSTIC PARAMETERS AND AGGRESSIVE THERAPY (MEETING ABSTRACT).

Brodsky I, Fuscaldo KE, Strayer DR, Kahn SB, Conroy JF
Department of Hematology/Medical Oncology, Hahnemann Hospital, 230 North Broad Street, Philadelphia, PA, 19102
Proc Am Soc Clin Oncol; 1:C-478 1982

Thirty-three patients have been entered into our study since its inception. The prognostic indicators at diagnosis do not seem to correlate with length of survival which in this series continued to be about 72 months (estimated median survival). Of particular interest has been the presence of high levels of a DNA polymerase in platelets of these patients. This DNA polymerase is contained in small particles with a buoyant density of about 1.2 gm/ml and is capable of supporting reverse transcription. This activity was first observed in polycythemia vera, essential thrombocythemia and myelofibrosis, but the highest levels are found in CML. The involvement of retroviral parameters in CML led to the consideration of interferon as a treatment modality. One patient, treated first with a novel mismatched dsRNA interferon inducer rIn.r(C12,U)n had an objective response for approximately 6 months. Subsequently, fibroblast interferon (total dose 20 million units) was given. A partial remission was obtained with reversal of an abnormal clone. (no Refs)

72. DIFFERENTIAL CYTOTOXICITY OF SOME FLUORINATED DERIVATIVES AGAINST HUMAN LEUKEMIC CELL LINES (MEETING ABSTRACT).

Srivastava BI, Alderfer JL
Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:854 1982

Among several fluorinated derivatives examined, 2-fluoroadenine, 5-fluorocytidine and 5-fluorodeoxyuridine were equally cytotoxic to T- and B-cell lines, 5-fluorouracil was preferentially cytotoxic to B-cell lines and arabinosyl 5-fluorocytidine and poly 5-fluorouridylic acid to T-cell lines. Poly 5-fluorouridylic acid also differentially inhibited DNA polymerase alpha, beta and gamma and RNA polymerase II from human leukemic cells as well as viral reverse transcriptase and herpes simplex virus DNA polymerase but it did not inhibit terminal transferase or poly (ADP-ribose) polymerase. Although poly U and poly 2'-fluoro-2'-deoxyuridylic acid also inhibit the above DNA polymerases, these compounds or 5-fluorouridylic acid were not cytotoxic to human T- and B- leukemic cell lines. Poly 5-fluorouridylic acid, like poly-araCMP and poly-araAMP is selective and more cytotoxic than the parent compound. These compounds should have important chemotherapeutic potential, due to their preferential uptake by tumor cells via pinocytosis and their action as template/primer analogs or depot of activated drug. (1 Ref)

73. POTENT ANTIVIRAL 2'-FLUORO-ARABINOSYL PYRIMIDINE NUCLEOSIDES: LACK OF MUTAGENIC ACTIVITY.

Marquardt H, Westendorf J, Marquardt H

Dept. Toxicology, Univ. Hamburg Medical Sch., Grindelallee 117, 2000 Hamburg 13, W. Germany

Carcinogenesis; 3(5):593-596 1982

The carcinogenicity of many drugs, such as antitumor agents, is a subject of growing concern. The newly developed pyrimidine nucleosides, 2'-fluoro-5-iodo-1-beta-D-arabinofuranosylcytosine (FIAC) and 2'-fluoro-1-beta-D-arabinofuranosyl-5-methyluracil (FMAU), have shown potent antiherpes virus activity in tissue cultures, laboratory animals and man and an activity to inhibit the growth of certain tumor cell lines in vitro. Radioactivity of 14C-labeled FIAC and FMAU is incorporated into the DNA of normal and neoplastic mammalian tissues. However, we now report that FIAC and FMAU are inactive in a bacterial mutagenesis assay (Salmonella-microsome test) and in a mammalian cell mutagenesis assay employing V79 Chinese hamster cells in vitro. Both agents did not induce unscheduled DNA synthesis in primary Wistar rat hepatocytes in vitro. (Author abstract) (7 Refs)

74. INHIBITORY EFFECT OF E-5-(2-BROMOVINYL)-1-BETA-D-ARABINOFURANOSYLURACIL ON HERPES SIMPLEX VIRUS REPLICATION AND DNA SYNTHESIS.

Descamps J, Sehgal RK, De Clercq E, Allaudeen HS

Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510

J Virol; 43(1):332-336 1982

The effect of E-5-(2-bromovinyl)-1-beta-D-arabinofuranosyluracil (BVaraU) on herpes simplex virus (HSV) replication was examined and compared with that of E-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd). The 50% inhibitory dose against HSV type 1 (HSV-1) was 0.1 ug/ml compared with 0.008 ug/ml for BVdUrd; the antimetabolic 50% inhibitory dose of BVaraU ranged from 20 to 95 ug/ml. The addition of 50 ug of BVaraU per ml to HSV-1-infected Vero cells decreased the synthesis of viral and cellular DNA by 37 and 28%, respectively. The 5'-triphosphate (BVaraUTP) competed with dTTP in DNA synthesis by the herpes-viral and cellular DNA polymerases; the apparent Ki values of HSV-1 DNA polymerase, DNA polymerase alpha, and DNA polymerase beta were 0.14, 0.32, and 5 uM, respectively. Thus, BVaraU was a less effective antiherpesvirus agent than BVdUrd; unlike BVdUrd, it did not appear to be internally incorporated into replicating DNA in virus-infected cells. (Author abstract) (13 Refs)

75. EFFECTS OF BENZO[A]PYRENE DIOL EPOXIDE ADDUCTS ON DNA SYNTHESIS IN MAMMALIAN CELLS.

Rinaldy A, Lockhart ML, Deutsch JF, Ungers GE, Rosenberg BH
Walker Lab., Sloan-Kettering Inst., Rye, NY, 10580
Mutat Res; 94(2):383-391 1982

Effects of benzo[a]pyrene diol epoxide (BPDE) adducts in DNA were studied in CV1-P cells infected with SV40 virus treated with BPDE in vitro prior to infection. Replication in CV-1 monkey kidney cells of SV40 DNA containing an av of 11 anti-BPDE adducts/molecule were compared to that of similar DNA containing no adducts. The decreased replication of DNA from BPDE-treated virus may have resulted directly from the presence of BPDE adducts in the DNA, or it may have been due to a decrease in cellular uptake or uncoating of the virus, possibly caused by the presence of BPDE adducts in the viral capsid proteins. Although replication of the DNA of the BPDE-treated virus was initially low, in the course of time the ratio of treated tsA to deletion molecules approached that of the mock-treated control. Viruses with 11 adducts/DNA molecule were only approx 12% viable in spite of the fact that most or all of the DNA molecules are ultimately able to replicate. The loss of viability thus suggested either a persistent defect in transcription of the infecting DNA, caused by BPDE adducts that do not prevent replication and/or a high probability of producing defective progeny molecules during repair or bypass replication of parental molecules containing BPDE adducts. The 12% viability indicated an av of approx 2/11 lethal hits. Data for three adducts/molecule indicated that approx 7% of the adducts were lethal. Results implied that a minor adduct might be responsible for the the loss of viability. (19 Refs)

76. DIFFERENTIAL EFFECTS OF HYDROXYUREA ON THE SURVIVAL OF UV- AND MNNG-TREATED ADENOVIRUS 5.

Day RS, Ziolkowski CH
Nucleic Acid Section, LMC, DCCP, NCI, NIH, Building 37, Room 3C23, Bethesda, MD, 20205
Mutat Res; 94(2):257-262 1982

Effects of hydroxyurea (HU) on the survival of both UV- and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treated adenovirus 5 when used to infect either human cell strains XP12BE, CRL1220, XP4BE, and KD were studied and observed that HU decreased in all cases studied the survival of UV-irradiated adenoviruses. A 24-hr 10-milliM (mM) HU postinfection treatment of XP12BE fibroblasts caused apparent increase in sensitivity of UV-irradiated adenovirus 5. The magnitude of inhibition of viral recovery by HU, however, was less than that observed when infecting normal fibroblasts. In the presence of HU, the lethality of a given dose was increased by a factor of 2.1 in normal, cells, and by 1.29 using the XP12BE strain. In ancillary experiments, 10 mM HU present with KD cells only during the 24 hr prior to infection caused no enhancement of viral inactivation. HU (10 mM) applied to CRL1187 or KD normal fibroblasts (Mer+) infected with MNNG-treated adenoviruses caused no change in viral survival indicating that HU dose not interfere greatly with the Mer repair pathway. However, HU treatment did increase the survival of MNNG-treated viruses when infecting the A1336 and A172 Mer- strains, the lethality of a given dose being increased by 1.52 +-0.10. The result showed that viral recovery occurring independently of the Mer system is somewhat susceptible to blockage by the HU treatment. (26 Refs)

GENERAL REVIEWS

77. HUMAN HERPESVIRUS INFECTIONS: CLINICAL ASPECTS.

Glaser R, Gotlieb-Stematsky T
Ohio State Univ. Coll. Medicine, Columbus, OH
Human Herpesvirus Infections: Clinical Aspects. New York, Marcel Dekker Inc., 280 pp., 1982.

Clinical aspects and treatment of infections resulting from human herpes viruses, including herpes simplex virus (HSV) I and II, human cytomegalic virus (HCV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) are discussed. The pathogenesis, pathology, clinical manifestations, laboratory diagnosis, treatment, and epidemiology of HSV and the association of HSV II with cervix neoplasia are discussed. Clinical syndromes, specific organ involvement, prevention, and treatment of HCV infections are considered. Topics discussed in relation to VZV infections include primary infection with VZV, intrauterine infections with VZV, reactivation of VZV infections, epidemiology of VZV infection, and laboratory evaluation of VZV infection modalities. The relationship of EBV to infectious mononucleosis (IM) is described. The association of EBV with neurologic diseases is considered: comparative pathology of EBV and other herpesviruses; clinical features of IM; complications of IM and EBV infections; neurologic complications; cranial neuropathies and Bell's palsy; myelitis; mononeuritis; Guillian-Barre syndrome (GBS); GBS and IM; subacute sclerosing panencephalitis, multiple sclerosis, and EBV; possible psychological manifestations associated with EBV infection; manifestations in the cerebral spinal fluid; and possible mechanisms of neurologic manifestations of EBV-associated infection. Use of antiviral drugs, vaccines, and immunotherapy in the treatment of human infections due to herpesviruses is considered. (1064 Refs)

78. INFECTIONS IN CANCER PATIENTS. MONOGRAPH SERIES OF THE EUROPEAN ORGANIZATION FOR RESEARCH ON TREATMENT OF CANCER. VOLUME 10.

Klastersky J
Service de Medecine, Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, 1000 Brussels, Belgium
Monogr Ser Eur Organ Res Treat Cancer 10: 220 pp., 1982.

Prevention and treatment of opportunistic infections in cancer patients are reviewed. Presentations include predisposing factors to fungal and viral infections in cancer patients, mechanisms of acquisition and development of bacterial infections in cancer patients, usefulness and limitations of animal models in the study of opportunistic nonbacterial infections, laboratory diagnosis of opportunistic viral infections, laboratory diagnosis of fungal and parasitic disease in patients with neoplastic disease, gut resistance to colonization, infection prevention in cancer patients, approaches to therapy of bacterial infections in the granulocytopenic patient, cryptococcal meningitis and other fungal infections of the CNS in cancer patients, significance and clinical manifestations of fungemia, role of empiric antifungal therapy for granulocytopenic cancer patients with persistent fever, diagnostic and therapeutic approach to nonbacterial pneumonia in immunodepressed patients, spectrum of herpesvirus infections in immunosuppressed patients, and chemotherapy and immunotherapy of opportunistic viral infections. (824 Refs)

79. RECENT ADVANCES IN HISTOPATHOLOGY.

Anthony PP, MacSween RN
Royal Devon Hosp., Exeter, England
Recent Adv Histopathol (11): 287 pp., 1981.

Recent advances in clinical histopathological practice and some technical aspects are reviewed. Topics include diseases in the ancient world, the multistep theory of neoplasia, papillomaviruses and cancer, pathology of dementia, perinatal autopsy, some aspects of pulmonary pathology, pseudomembranous and infective colitis, pathology of female infertility, the infertile testis, gestational tumors of trophoblast, cystic diseases of the kidney and reflux nephropathy, metabolic bone disease, the solitary thyroid nodule, the conjunctival biopsy, road traffic accidents, diagnostic electron microscopy, and fine needle aspiration cytology. The multi-step theory of neoplasia is discussed with respect to nature and development of human cancer, multi-step hypothesis for cancer development (CD), sequential analysis of CD (experimental animals and humans), sequential analysis of liver as a model for carcinogenesis, and implications of multi-step theory for cancer diagnosis, prevention, and control. Various papillomas occurring in cattle and in man are examined, and evidence that papillomavirus may be implicated in the same naturally occurring carcinomas is reviewed. Aspects of pulmonary pathology including shock lungs, legionnaires' disease, prelymphomatous changes in the lung, bronchocentric granulomatosis, and necrotizing sarcoid granulomatosis are discussed. The role that infective agents play in inflammatory diseases of the large intestine is investigated. Important advances have been achieved with respect to etiology of pseudomembranous colitis and isolation of new pathogens from patients with acute diarrhea. More speculative is the research implicating microorganisms in the etiology of ulcerative colitis and Crohn's disease. (967 Refs)

OTHER RELATED STUDIES

80. NATURAL ANTIBODY TO A HUMAN BLADDER CANCER CELL LINE (MEETING ABSTRACT).

Grossman HB
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Sera from 144 healthy blood donors were screened for naturally occurring antibody against the bladder carcinoma cell line RT4 using an immune adherence (IA) assay. One hundred twenty-four had no titer at 1/4 dilution; 18 had a titer of 1/4; and one had a titer of 1/16. Only one serum (9241) exhibited high titer with reactivity at a dilution of 1/124. Qualitative and quantitative absorptions were performed with a wide variety of cells to characterize the specificity of the reaction. Aliquots of absorbed serum were tested for residual IA activity on RT4 target cells. Reactivity was absorbed by the bladder carcinomas RT4 and 5637 and the lung carcinoma SK-LC-LL. Antigens related to fetal bovine serum were eliminated because RT4 cells grown in human A positive serum for five passages completely absorbed the activity of serum 9241 for RT4. Other bladder carcinoma cell lines and other malignant cell lines did not abrogate reactivity. Similarly, cultured normal kidney cells, fibroblasts, fetal cells, xenogeneic cells, and Epstein-Barr virus transformed lymphoblasts did not remove reactivity. Non-cultured erythrocytes and three surgically obtained specimens of human urothelium did not absorb reactivity of serum 9241 for RT4. One urothelial specimen from a patient with transitional cell carcinoma of the ureter completely removed reactivity. The antigen defined by serum 9241 for RT4 is heat stable and trypsin resistant as demonstrated by complete absorption with either heated or trypsinized RT4 cells. Quantitative absorption analyses showed that RT4, 5637, and SK-LC-LL present an equal amount of antigen(s) per cell as defined by serum 9241. (no Refs)

81. DEVELOPMENT OF NON-HODGKIN'S LYMPHOMA SUBSEQUENT TO MARROW TRANSPLANTATION (MEETING ABSTRACT).

Hackman RC, Schubach WH, Neiman PE, Miller G, Thomas ED
Division of Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

We have noted the development of a malignant solid tumor in two of approximately 850 marrow allograft recipients. Both have been non-Hodgkin's lymphomas of B lymphocytes. One was an immunoblastic sarcoma identified at autopsy in a 5-year-old male 56 days after marrow grafting for acute lymphoblastic leukemia. The donor was his sister who was HLA-mismatched at one A locus. Moderate acute graft versus host disease (GVHD) had been documented by skin biopsy. Immunoperoxidase staining of the tumor demonstrated only intracytoplasmic lambda light chains. By cytogenetic analysis and by blot hybridization of a highly polymorphic locus in human DNA, the tumor was of donor cell origin. Blot hybridization studies of tumor DNA demonstrated at least 70 per cent of the Epstein-Barr (EBV) genome at about 7 genome-equivalents per cell. The other tumor was an apparently isolated histiocytic lymphoma (large, noncleaved, follicular center cell lymphoma) resected from the lumbar epidural space 500 days following allografting of a 25-year-old male for myelofibrosis. The donor was his HLA-matched brother. Clinical acute GVHD had not been documented. The tumor was monoclonal and of host origin. These two cases differ in pretransplant diagnosis, development of clinical GVHD, tumor histology, and tumor genetic origin. (no Refs)

82. CHROMOSOMAL ABERRATIONS IN CHRONIC B-CELL LYMPHOCYTIC LEUKEMIA.

Gahrton G, Robert KH
Dept. Medicine, Karolinska Inst., Huddinge Univ. Hosp., S-141 86 Huddinge, Sweden
Cancer Genet Cytogenet; 6(2):171-181 1982

Production, incidence, and types of chromosome aberrations in chronic B-cell lymphocytic leukemia (B-CLL) are reviewed. Of polyclonal B-cell mitogens, Epstein-Barr virus and lipopolysaccharide from E coli have been the most successful for cytogenetic analysis of B-CLL. The mitogenic responses measured by 3H-labeled thymidine incorporation into leukemic cells and the mitotic index are variable. Difficulties associated with calculating reliable incidence figures for chromosomal aberrations in B-CLL are considered. In B-CLL, both numerical and structural aberrations are found. The most common numerical aberration is an extra chromosome 12. Other aberrations include deletion of chromosome 14, translocations, deletions, and other extra chromosomes. Many of the chromosomal abnormalities seen in B-CLL have also been found in other malignant hematopoietic disorders, particularly lymphoproliferative disorders. However, the most common abnormality, the extra chromosome 12, is rare in other disorders. The biological significance and prognostic importance of chromosomal aberrations in B-CLL are discussed. (72 Refs)

83. SURVIVAL OF 60CO-IRRADIATED HERPES SIMPLEX VIRUS IN 15 HUMAN DIPLOID FIBROBLAST CELL STRAINS.

Zamansky GB, Little JB
Dept. Microbiology, Boston Univ. Sch. Medicine, 80 E. Concord St., Boston, MA, 02118
Mutat Res; 94(2):245-255 1982

Survival of gamma-irradiated herpes simplex virus (HSV) was investigated in cells from patients with ataxia telangiectasia (AT), hereditary retinoblastoma, Gardner's syndrome, Fanconi's anemia, and xeroderma pigmentosum (XP). Survival of 60Co-irradiated HSV in normal cells at-75 C was much greater than that of virus irradiated at 4 C. Under the more resistant conditions, approx a 2.5-fold greater dose was required to reduce survival to 1%. Survival of 60Co-irradiated HSV in cell strains derived from diseases associated with DNA repair deficiencies at-75 C was greatly increased if compared with that obtained for repair at the higher temperature (4 C). Survival generally declined more rapidly at lower doses. Only in two cell strains did the survival of HSV differ significantly from that in normal controls. The D0 values (the dose necessary to reduce survival to 37% on the linear portion of the survival curve) for the complementation group A XP strain XP12BE were approx 20% lower than those of controls, regardless of the irradiation conditions. Fanconi's anemia strain was the only cell which exhibited a significantly higher level of virus survival. No significant changes in plaque-forming ability of unirradiated and irradiated (300 kilorad) virus were observed when treatment occurred immediately prior to infection. (39 Refs)

84. INFLUENCE OF B LOCUS ON AVIAN VIRAL INDUCED TUMORS.

Cauchy L, Dambrine G, Coudert F
Station de Pathologie aviaire et de Parasitologie, I.N.R.A., Centre de Recherches de Tours-Nouzilly, F-37380 Monnaie, France
Bull Cancer (Paris); 69(2):194-198 1982

Since early in the century Avian Cancers were described as induced by viruses which later were known of DNA and RNA types. The susceptibility of birds was found different according to the genetic lines of the chickens and specially to the B locus blood group. since the B locus of birds was strongly associated with the Major Histocompatibility Complex (MHC) it was of interest to review the last reports on the influence of the B locus on viral induced tumors. In Marek's Disease due to a DNA virus (Herpes type) the B21 allele expresses the greater resistance compared with other B alleles although non-B factors could be involved as demonstrated with the lymphocyte factor Ly-4. The possible mechanisms of the influence of B locus on the resistance against Marek's Disease are discussed. The tumors induced by RNA viruses (Avian Leucosis Sarcomas) develop or regress following genetic characters closely related to MHC. Differences of resistance exist between B alleles. Complementary genes should be present to fully express the resistance. The relationship between MHC-B locus and resistance to tumors stimulates the actual assays. Since a number of parameters remain still unknown further research should be done in order to evidence the involved mechanisms of the resistance. (Author abstract) (26 Refs) (In FRE)

85. HERPES ZOSTER (HZ) IN PATIENTS (PTS) WITH LUNG CANCER (MEETING ABSTRACT).

Feld R, Evans WK, DeBoer G
The Princess Margaret Hospital, Toronto, Ontario M4X 1K9, Canada
Proc Am Soc Clin Oncol; 1:C-218 1982

HZ is a frequent complication of hematological malignancies, but is rarely seen in association with solid tumors. In a trial conducted from 1976-78, we observed that 13 of 161 pts with small cell carcinoma of the lung (SCCL) developed HZ as a complication of therapy. These pts had been treated with 3 courses of induction chemotherapy with IV cyclophosphamide (750 mg/m(2)), doxorubicin (50 mg/m(2)) and vincristine 2 mg q 3 weeks, followed by 2,500 rads in 10 treatments to the pre-chemotheray intrathoracic disease. Pts then received intermittent oral CCNU (lomustine), methotrexate and procarbazine for 1 year (CAV-1). From 1978-80, 250 pts with SCCL were treated on a second prospective trial and only 4 developed HZ. Induction therapy in this study consisted of 6 courses of cyclophosphamide (900 mg/m(2)), doxorubicin (45 mg/m(2)) and vincristine 2 mg, followed by intrathoracic and cranial irradiation (CAV-2). Pts did not receive maintenance chemotherapy. A retrospective analysis of 6,576 pts with lung cancer treated from 1962-75 revealed that 10 of 622 pts with SCCL developed HZ, as compared to 48 of 5,954 pts with non-SCCL. The cumulative probability of developing HZ at various times using the Wilcoxon-Gehan test revealed the risk of developing HZ on CAV-1 to be significantly greater than the retrospective group and also greater than CAV-2; however, there is no significant difference between the historical group and CAV-2. (no Refs)

86. EFFECT OF HUMAN FIBROBLAST INTERFERON ON NATURAL KILLER CELL ACTIVITY: STIMULATION IN VITRO AND INHIBITION IN VIVO.

Heidemann E, Reichmann U, Wilms K, Treuner J, Niethammer D
Abt. Innere Medizin II, Med. Univ.-Klinik, Otfried-Muller-Str., D-7400 Tubingen, W. Germany
Klin Wochenschr; 60(12):625-629 1982

This paper describes the influence of human fibroblast interferon (IFN-beta) on the cytotoxic activity of natural killer cells (NK) in vitro and in vivo using the blood of healthy donors and myeloma patients. IFN-beta stimulates NK activity against all target cells tested in vitro in a dose-dependent way up to 250% of pretreatment values. At higher IFN concentrations, stimulation returned to baseline values. Stimulation was most pronounced in the lowest lymphocyte to target cell ratio. 1-to 2-h preincubation of effector cells with IFN was enough to achieve maximal stimulation. The effector cells of IFN-treated myeloma-patients, or patients with herpes zoster, showed a clear reduction of toxicity against all cells tested during the first infusion, as compared to the pretreatment values. (Author abstract) (22 Refs)

87. CYTOMEGALOVIRUS IMMUNE PLASMA IN BONE MARROW TRANSPLANT RECIPIENTS.

Winston DJ, Pollard RB, Ho WG, Gallagher JG, Rasmussen LE, Huang SN, Lin CH, Gossett TG, Merigan TC, Gale RP
Div. Infectious Diseases, Dept. Medicine, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
Ann Intern Med; 97(1):11-18 1982

The effects of passive immunization on cytomegalovirus infection and interstitial pneumonia in marrow transplants were evaluated in a randomized, controlled trial. Twenty-four patients received cytomegalovirus immune plasma before and after transplantation, and 24 patients were controls. Although the incidence of cytomegalovirus infection was similar in the control and plasma groups, symptomatic infection (12 of 24 versus 5 of 24, $p = 0.07$) and interstitial pneumonia (11 of 24 versus 5 of 24, $p = 0.12$) occurred less frequently in the group receiving plasma. Cytomegalovirus infection occurred in 11 of 13 recipients of leukocyte transfusions and in 16 of 35 patients not given leukocyte transfusions ($p = 0.02$). Among patients not given leukocyte transfusions, the incidence of cytomegalovirus infection was similar in the control and plasma groups, but symptomatic infection (8 of 18 versus 1 of 17, $p = 0.03$) and interstitial pneumonia (9 of 18 versus 1 of 17, $p = 0.01$) were significantly less in the group receiving plasma. These results suggest that passive immunization modifies cytomegalovirus infection in humans and prevents interstitial pneumonia in marrow transplants, especially when leukocyte transfusions are not used. (Author abstract) (39 Refs)

88. INFECTIOUS COMPLICATIONS IN LEUKEMIC PATIENTS.

Bodey GP, Bolivar R, Fainstein V
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Semin Hematol; 19(3):193-226 1982

Recent advances in understanding the pathobiology of infectious complications occurring in patients with acute leukemia, their respective prognoses and their treatment are reviewed. Topics discussed include factors associated with infection (leukopenia, abnormal neutrophil function, myelosuppression), new organisms and changing patterns of infection (Staphyloccoccus aureus, S epidermis, legionella pneumophila, JK bacteria, Corynebacterium species, Clostridium difficile, Capnocytophaga ochracea) approaches to diagnosis of infection (bacterial, fungal, viral), management of infection (antibiotic schedule, antibiotic synergism, new antibiotics, antifungal and antiviral agents), and prophylaxis of infection (granulocyte transfusion, bone marrow transplantation, lithium carbonate, immunotherapy, Pseudomonas vaccine, pneumococcal polysaccharide vaccine, cytomegalovirus vaccine, varicella zoster vaccine, passive immunotherapy, hepatitis immune globulin, antisera to gram-negative bacteria, transfer factor, interferon, immunomodulators). (256 Refs)

89. CHROMOSOMES OF HUMAN HEPATOMA CELL LINES.

Simon D, Aden DP, Knowles BB
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Int J Cancer; 30(1):27-33 1982

The karyotypes of three human hepatoma cell lines Hep G2, Hep 3B and PLC/PRF/5 were investigated by G-and C-banding techniques. In addition to ploidy changes, typical for most carcinoma cell lines, certain markers were found that remained stable throughout passage of these cultures. Chromosome 1 is involved in multiple translocations, resulting in at least three copies of the chromosome 1 heterochromatin region in each cell line. Inversion in the 9qh region is also seen. In addition, each of the cell lines consistently contains trisomy of 17q. The rearrangements of chromosome 1 are more striking in the Hep 3B and PLC/PRF/5 cell lines, which are derived from human hepatocellular carcinomas and contain integrated copies of the hepatitis B viral genome. These two cell lines are characterized by the presence of at least five copies of the 1 (p13 to q21) region that result from multiple deletions and/or translocations; by consistent trisomy and polymorphism of the 9qh region; and by trisomy of chromosome 10 (also involved in rearrangements). The Hep G2 and Hep 3B cell lines behave functionally as highly differentiated liver parenchymal cells and are karyologically distinguishable from PLC/PRF/5 both by the presence of trisomy of 6 (pter to q14) and by the finding that one of the homologues of chromosome 15 is 15q+. (Author abstract) (29 Refs)

90. TREATMENT OF ADVANCED MALIGNANT HEPATOMA WITH ADRIAMYCIN OR AMSA IN COMBINATION WITH VM 26 + 5 FU (MEETING ABSTRACT).

Bezwoda WR, Darman DP
University of the Witwatersrand, Parktown, South Africa
Proc Am Soc Clin Oncol; 1:C-353 1982

Forty-seven patients suffering from malignant hepatoma have been entered into a series of ongoing studies of the effect of chemotherapy in the treatment of this disease. Of these 46 patients were suffering from hepato cellular cancer and one from a cholangio-carcinoma. Forty two patients were males with a median age of 32 years. The majority had evidence of previous infection with hepatitis B virus, persistent surface antigenemia, disturbed liver function tests and underlying cirrhosis. Liver involvement was extensive involving both lobes in all patients and spread beyond the liver was seen in 7 patients. The first treatment regimen consisted of a combination of VM 26 100 mg/m2 IV X 3, Adriamycin 60 mg/m2 IV X 1 and 5 Fluorouracil (5 FU 500 mg/m2 IV X 3). Responses were seen in 11/23 patients. Following this preliminary study a randomized trial comparing VM 26 + Adriamycin + FU with VM 26 + amsacrine (AMSA) + 5 FU was started. Of 24 patients treated, 5/13 and 4/11 respectively were judged to have responded to treatment. The median duration of survival in responding patients was significantly increased compared to non responding patients. Two patients are alive greater than 15 months. Quantitative alpha fetoprotein estimation has been helpful in monitoring the response of patients to treatment. (no Refs)

91. EFFECT OF NUCLEASE S1 ON DNA OF HIGHLY ONCOGENIC SIMIAN ADENOVIRUS SA7(C8).

Zavizion BA, Naroditskii BS, Grodnitskaia NA, Makhov AM, Tikhonenko TI
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Mol Biol (Mosk); 16(3):569-574 1982

Comparative evaluation of the effects of nuclease S1 on DNA and on complex of DNA with terminal protein of adenovirus SA7 showed the cleavage of the terminal protein only after preliminary hydrolysis. Treatment with nuclease S1 resulted in 5-10x decrease of the infectivity of DNA. (22 Refs) (In RUS)

92. ANALYSIS OF PLUME EMISSIONS AFTER PAPOVAVIRUS IRRADIATION WITH THE CARBON DIOXIDE LASER.

Bellina JH, Stjernholm RL, Kurpel JE
Laser Res. Foundation, 3439 Kabel Drive, Suite 7, New Orleans, LA, 70114
J Reprod Med; 27(5):268-270 1982

The viability of vaporized material emanating from irradiation of Papovavirus tumors was assessed by metabolic DNA replication, and RNA transcription studies. Material collected from the vapor plumes from condylomata acuminata lacked metabolic activity, and replication or transcription could not be demonstrated using labeled nucleosides. Cytologic evaluation showed very few intact cells; cell membranes were dehydrated, and nuclei appeared shrunken and pyknotic. (4 Refs)

93. PARANEOPLASTIC NEUROLOGICAL SYNDROMES.

Dounes AV
No affiliation given
Rev Asoc Med Argent; 94(5/6):135-138 1981

Definitions and descriptions of paraneoplastic neurological syndromes are discussed. This syndrome includes a group of symptoms which is linked to the development of a malignant tumor yet not necessarily a mechanical or metastatic consequence of the tumor. The syndrome is associated most frequently with the following neoplasms; oat cell carcinoma, bronchiogenic carcinoma, occasionally with ovarian, prostatic and breast neoplasms, Hodgkin's lymphoma and multiple myeloma. There are several theories on the etiology of this syndrome. There is the possibility of an allergic reaction of the central or peripheral nervous system or the muscular system to a substance secreted by the tumor. A secreted substance could also cause a toxic reaction. The Denny-Brown hypothesis states that the tumor might secrete substances which compete with enzymes and coenzymes that are indispensable to the normal functioning of the nervous system. According to Henson, the etiology might be viral. There are six common neurological syndromes; Denny-Brown polyneuritis, Wyburn-Mason sensitive matrix neuropathy, polymyositis, dermatomyositis and carcinomatous myopathy. A comparative table of myasthenia gravis and myasthenic syndrome symptoms is discussed in relation to differential diagnosis. Other aspects of this syndrome are cerebral cortex degeneration, encephalopathies, amyothrophic lateral sclerosis, Herpes zoster and combined degeneration of the medulla. (26 Refs) (In SPA)

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VIRUS ISOLATION/ STRUCTURE/ CHARACTERIZATION/ IDENTIFICATION

1. TRANSMISSION AND SCANNING ELECTRON MICROSCOPIC STUDIES OF HERPES VIRUSES.

Nii S
Dept. Virology, Okayama Univ. Medical Sch., Okayama, Japan
Excerpta Med Int Congr Ser; 571:3-11 1982

Electron microscopic (EM) studies of various herpesviruses (HPVs) are presented: ultrastructure of virions of HPV, morphological variability of intranuclear virus particles correlated with their development, variable appearance of viral cores among members of the HPV family, envelopment, particles observed on the surface of cells infected with HPVs, and time-sequence studies on the appearance of viral particles on the surface of cells infected with herpes simplex virus (HSV). From a time-sequential study and EM observations of cells infected with several HVPs, a hypothesis is proposed concerning the assembly of intranuclear particles. Differences noted in the appearance of viral cores of different HVPs (Varicella-zoster virus, HPV of turkey [HVT], human cytomegalovirus [HCMV]) indicate inherent differences in their ultrastructure.

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In vitro cultured cells infected with various HPVs examined by scanning electron microscopy showed particles 170-200 nanometer in diameter in 5/8 HPV examined: HSV-1, HSV-2, VZV, HCMV and infectious laryngo-tracheitis virus. In the time-sequence studies, many virions of HSV attached to the surface of infected cells. The mechanism of this phenomenon appears to be closely related with that of egress of the virus. (9 Refs)

2. HERPES VIRUS SPECIFIC ENZYMES: PROPERTIES, PHYSIOLOGICAL ROLES, AND PHARMACOLOGICAL IMPLICATIONS.

Cheng YC, Nakayama K, Derse D, Bastow K, Ruth J, Tan RS, Dutschman G, Caradonna SJ, Grill S
Dept. Pharmacology, Sch. Medicine, Univ. North Carolina, Faculty Lab. Office Building 231-H, Chapel Hill, NC, 27514
Excerpta Med Int Congr Ser; 571:47-56 1982

After infection of cells with various types of herpes virus, a number of new polypeptides are synthesized, a few of which exhibit specific enzyme activity. A number of enzymes (thymidine kinase, DNA polymerase, DNase, ribonucleotide reductase, deoxyuridine triphosphatase, and uracil-DNA-glycosylase) are discussed in relation to their role as potential targets for selective antiviral compounds. (79 Refs)

3. AUGMENTED IMMUNOGENICITY OF LEWIS LUNG CARCINOMA BY INFECTION WITH HERPES SIMPLEX VIRUS TYPE 2.

Reiss-Gutfreund RJ, Nowotny NR, Dostal V, Wrba H
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Eur J Cancer Clin Oncol; 18(6):523-531 1982

In vitro, LLT cells sustain HSV-2 replication without evidence of lysis. Simultaneously, multiplication of the cells is stimulated. These xenogenized cells were tested for their immunopotentiating capacity: three-step immunization with xenogenized viable cells conferred significantly augmented transplantation resistance to a challenge graft with 4 x 10(4) intact LLT cells. Latency periods preceding tumor formation were increased and 15% of the mice failed to form primary tumors. Metastasis was likewise decreased and 25% of the mice had healthy lungs. Immunopotentiation, however, did not suffice to significantly protect against a challenge with 6 x 10(4) intact cells. The presence of virus-specific neoantigens on HSV-2-infected viable cells was demonstrated by the progressively increasing number of rejections of 4 x 10(4) xenogenized cells during the successive immunization steps. Immunization with non-viable LLT cells did not augment resistance to challenge. (Author abstract) (31 Refs)

4. EVIDENCE FOR TWO CLASSES OF CHROMATIN-ASSOCIATED EPSTEIN-BARR VIRUS-DETERMINED NUCLEAR ANTIGEN.

Spelsberg TC, Sculley TB, Pikler GM, Gilbert JA, Pearson GR
Dept. Cell Biology, Section Biochemistry, Mayo Clinic, Rochester, MN, 55901
J Virol; 43(2):555-565 1982

A new class of Epstein-Barr virus nuclear antigen (EBNA) was identified by the complement fixation assay. This new species of EBNA is more tightly bound to chromatin and was termed Class II EBNA, as opposed to the more weakly associated species, Class I EBNA. Preparations of this new antigen(s) specifically reduced absorption with the titer of anti-EBNA antibodies as determined by the anticomplement immunofluorescence assay. Therefore, the complement fixation antigens (Class II EBNA) appear to be related to the classical EBNA (Class I EBNA). The Class I EBNA was found to focus at the same pH (4.6) as the soluble antigen found in the cytosol. The Class II EBNA differed from the Class I EBNA with regard to its overall charge, molecular size, antigenicity, and affinity for chromatin. The Class II EBNA appeared to be a basic protein, based on its apparent pI of 9.2 and its binding to cation-exchange resins. It differed from histones with regard to its molecular size (mol wt between 60,000 and 70,000) and its elution from hydroxylapatite chromatography. Steps were taken to prevent proteolysis and artifacts in the immunological assays and in the overall charge estimation of the new antigen by nonspecific basic histone protein-acidic protein interactions. Both Class I and Class II EBNA were identified by radioimmunoelectrophoresis on two-dimensional polyacrylamide gels with pI values of 5.0 and 8.5, respectively, and a mol wt range of 60,000 to 70,000 for both. A lower-mol-wt antigen identified by molecular sieve chromatography appeared to be due to interference by histones in the immunoassays since it was not observed by the two-dimensional gel electrophoresis. Further characterization of this Class II EBNA is in progress. (Author abstract) (40 Refs)

5. ESTABLISHMENT AND CYTOLOGICAL CHARACTERISTICS OF TWO IN VITRO T-CELL LINES DERIVED FROM A CHILD WITH ACUTE LYMPHATIC LEUKEMIA AND A MAN WITH ADULT T-CELL LEUKEMIA IN JAPAN.

Nagasaka M, Maeda S, Mabuchi O, Takubo T, Nasu K, Wano Y, Sugiyama T
(c/o Maeda) Dept. Pathology, Kobe Univ. Sch. Medicine, Kusunoki-cho, Chuo-ku, Kobe 650, Japan
Int J Cancer; 30(2):173-180 1982

Two permanent T-cell leukemia lines designated KH-1 and KH-2 were established from the peripheral blood of a 9-yr-old boy with acute lymphoblastic leukemia and a 47-yr-old man with adult T-cell leukemia (ATL). No T-cell growth factor was used. KH-1 cells grew as single cells and KH-2 cells formed clusters in suspension culture. E-rosette formation, the absence of immunoglobulin determinants and Epstein-Barr-virus-associated nuclear antigen, and the presence of T-cell antigens revealed by monoclonal antibodies were characteristics of these cell lines as in other established T-cell leukemia lines. Chromosome analysis at the beginning revealed mosaic presence of cells with 46, XY, t(8q+; 15q-) and 46, XY which was later completely replaced by the latter karyotype in KH-1, and abnormal karyotype, 47, XY, +3, t(8q-; 10p+) was maintained throughout the period of in vitro passage in KH-2. The donor patient of KH-2 formerly lived in the south-western part of Japan where ATL is considered endemic and numerous type-C virus particles were detected electron microscopically, in KH-2 cell pellets. (Author abstract) (33 Refs)

6. PURIFICATION AND BIOLOGIC CHARACTERIZATION OF A MAJOR EPSTEIN BARR VIRUS-INDUCED MEMBRANE GLYCOPROTEIN.

Qualtiere LF, Chase R, Pearson GR
Dept. Microbiology, Univ. Saskatchewan, Saskatoon, Saskatchewan, S74 0W0, Canada
J Immunol; 129(2):814-818 1982

The Epstein Barr virus membrane antigen (MA) complex is composed of three major high mw glycoproteins designated gp 300/350, gp 200/250, and gp 85/90. In the experiments reported in this paper, the gp 300/350 glycoprotein was purified from MA-positive extracts prepared from the B-95-8 cell line. This was accomplished by tandem combination of ion-exchange and lectin chromatography. It was routinely possible to purify this glycoprotein 400-600-fold by this procedure. Sera from animals immunized with gp 300/350 purified by this approach neutralized EBV infectivity and mediated antibody-dependent cellular cytotoxicity (ADCC) demonstrating that both of these important antigenic determinants were expressed on this glycoprotein. The presence of an ADCC determinant on this molecule was further substantiated by the finding that monoclonal antibody to gp 300/350 blocked ADCC mediated by a human ADCC antibody-positive reference serum. (Author abstract) (27 Refs)

7. RAPID DIAGNOSIS OF VIRUS INFECTIONS IN CHILDREN ON THERAPY FOR MALIGNANCIES (MEETING ABSTRACT).

Wood DJ, Corbitt G
Booth Hall Hospital, Manchester, England
Second International Symposium on Infections in the Immunocompromised Host, June 20-24, 1982 Stirling, Scotland The Upjohn Company; :A121 1982

Patients with malignancies (mainly acute lymphoblastic leukemia) attending a Regional Pediatric Oncology Unit have been thoroughly investigated for a viral etiology by appropriate virus isolation and serological tests when presenting with a possible infection. To date, 98 virus infections have been documented with virus isolation proving more sensitive than serology. Forty-six of ninety-eight (47%) of the virus infections documented have been caused by viruses commonly associated with problems in the immunosuppressed pediatric patient (Herpesvirus hominis, Herpesvirus varicellae, cytomegalovirus and measles-virus). The remainder have been associated with commonly occurring childhood viruses, and serious, sometimes life-threatening, infections have been seen with agents such as adenoviruses, respiratory syncytial virus, parainfluenza and influenza viruses, and mumpsvirus. On the basis of these results, rapid diagnostic tests, chiefly immunofluorescence of nasopharyngeal aspirates, but also electron microscopy of body fluids, have been introduced for many of the virus antigens. The performance of the rapid tests have been monitored in parallel with the standard techniques. Attempts have also been made to assess the value of the rapid tests developed in various clinical situations. Thus, the techniques developed have been shown to be capable of rapidly detecting the majority of virus infections involving the respiratory tract and skin or mucous membranes, but not those from children with pyrexia without an obvious focus of infection, although virus infection has been documented in 20% of such cases. (no Refs)

8. STRUCTURE OF ADENOVIRUS NUCLEOPROTEIN CORE STUDIED BY CIRCULAR DICHROISM AND SELECTIVE RADIOCHEMICAL LABELING.

Boulanger P, Loucheux-Lefevbre MH
Unite de Virologie Moleculaire de l'INSERM, U. 233, Place de Verdun, 59045 Lille Cedex, France
Biochem Biophys Res Commun; 107(2):470-480 1982

The conformational structure of wild-type adenovirus type 2 viral DNA (AV-DNA) within intact virion and adenovirus cores of different protein contents was studied by circular dichroism (CD) and by selective radiochemical labeling of some critical amino acids. Virus was grown on KB cells and was extracted in CsCl gradients. CD spectra were compared in intact virion and in deoxycholate and sarcosyl cores. AD-DNA was in highly condensed and packed conformation in both intact virus particles and deoxycholate cores, as found in chromatin nucleosomes. There were minor but significant CD spectral differences with eukaryotic chromatin which indicated that the adenovirus nucleosome-like structures had specific conformational features. AD-DNA complexed with protein VII in sarcosyl cores elicited a CD spectrum reminiscent of a relaxed DNA, which suggests that the adenovirus sarcosyl cores were no longer organized in nucleosome subunits. In parallel in vitro studies, the nature of the bonds involved in core structure was studied by selective labeling of some critical amino acids. The accessibility of lysyl and tyrosyl residues in adenovirus core proteins was investigated with the use of 14C-dansyl as a probe. Results suggest that core protein V was associated with protein VII mainly via hydrophobic bonds, and had a major role in the maintenance of the nucleosomal structure of the viral core. (34 Refs)

9. HYPOMETHYLATION OF HELA CELL DNA AND THE ABSENCE OF 5-METHYLCYTOSINE IN SV-40 AND ADENOVIRUS (TYPE 2) DNA: ANALYSIS BY HPLC.

Diala ES, Hoffman RM
Dept. Pediatrics, M-009, Univ. California at San Siego Sch. Medicine, La Jolla, CA, 92093
Biochem Biophys Res Commun; 107(1):19-26 1982

The extent of methylation in highly purified simian virus 40 (SV40) and adenovirus (type 2) DNA was investigated using a sensitive high pressure liquid chromatographic procedure. 5-Methylcytosine was not detected in virion SV40 DNA. This lack of methylation in SV40 contrasts to that in monkey kidney cells in which SV40 is propagated, in which 3.7% of all cytosines are methylated. 5-Methylcytosine was also not detected in adenovirus (type 2) DNA bases. In HeLa cells in which adenovirus is grown, 2.3% of cytosines were found to be methylated. This level of methylation is considerably lower than in normal and SV40-transformed human cells, which is about 3%. The contribution of DNA methylation to SV40 and adenovirus gene activity is discussed. (31 Refs)

10. THE BINDING OF SIMIAN VIRUS 40 LARGE T ANTIGEN TO THE POLYPHOSPHATE BACKBONE OF NUCLEIC ACIDS.

Montenarh M, Henning R
Dept. Biochemistry, Ulm Univ., P. O. Box 4066, D-7900 Ulm, W. Germany
Biochim Biophys Acta; 697(3):322-329 1982

Simian virus 40 (SV40) large tumor antigen (T antigen), a phosphoprotein found in nuclei of SV40-infected and -transformed cells, binds nonspecifically to DNA. To study this mechanism the binding properties of T antigen to double-stranded (ds) and single-stranded (ss) DNA-cellulose as well as to phosphocellulose were compared. After incubation of [35S]methionine or [3H]leucine/[32P]phosphate radioactively-labeled cell extracts at different pH values (6.0, 7.3, 9.0) with DNA- or phosphocellulose, bound and unbound species of T antigen were purified and analyzed by SDS-polyacrylamide gel electrophoresis for both the yield and the possible correlation with protein phosphorylation. T antigens bound with comparable affinities to ds- and ss-DNA-cellulose and phosphocellulose. These results suggest the binding of T antigen to the polyphosphate backbone of DNA as a molecular mechanism for its nonspecific binding. The evidence for this observation was supported by blocking the binding of T antigen to DNA-cellulose by divalent cations (Ca++, Mg++). 3H/32P ratios of T antigen obtained by double-labeling cells for various times imply that higher phosphorylated forms of T antigen bound more strongly to ds- and ss-DNA as well as to phosphocellulose. Thus, in the presence of cellular proteins and other components the binding activity of T antigen to the polyphosphate backbone of DNA seems to be positively correlated with its phosphorylation. These observations are consistent with the hypothesis that the binding affinities of SV40 T antigen to host cell DNA may be regulated by its phosphorylation. (Author abstract) (24 Refs)

11. SV40 A PROTEIN (T ANTIGEN) PHOSPHORYLATION.

Shaw SA
State University of New York at Stony Brook, New York, NY
Diss Abstr Int [B]; 42(11):4282-B 1982

A non-specific protease mapping procedure was developed to aid in the analysis of individual phosphorylation sites of the A protein. The A protein is phosphorylated at five or more sites. One phosphothreonine and four phosphoserine sites were distinguished. Several phosphorylation sites were mapped using T antigens encoded by deletion mutants. This method can be used to examine differentially phosphorylated A proteins in attempts to correlate structure with function. Examination of tsA58 A protein synthesized at the restrictive temperature demonstrated that phosphorylation occurred at the same sites as in wild type A protein, but a quantitative difference was seen in the phosphorylation of one phosphopeptide. Dephosphorylation did not affect the ability of the A protein to bind specifically to SV40 origin DNA. No differences were seen in the location, alignment, or affinity of the binding. It is, therefore, unlikely that phosphorylation at the majority of the phosphoserine sites is directly involved in the regulation of site-specific recognition and binding of the A protein to SV40 DNA. (no Refs)

12. CHARGE MICROHETEROGENEITY OF THE MAJOR CAPSID PROTEIN OF POLYOMA VIRUS.

Hare JD, King VL
Dept. Microbiology, Univ. Rochester Medical Center, Rochester, NY, 14642
J Virol; 43(2):456-464 1982

The behavior in isoelectric focusing of the major capsid polypeptide VP1 of several strains of polyoma virus was studied. Two previously recognized phenomena were reexamined, namely, (i) the separation of the VP1 polypeptide into multiple subspecies differing only slightly from each other in apparent isoelectric point and (ii) strain differences in the overall apparent net charge of the family of VP1 subspecies. It was found that the pattern of subspecies was reproducible when focusing was initiated from either the basic or acidic region of the gel, keeping the ampholyte mixture constant. However, individual subspecies were unstable, and labeled polypeptide could be shifted dramatically by either refocusing of separated subspecies or by altering the concentration of ampholytes. These findings suggest that protein-protein and protein-ampholyte interactions play an important role in the generation of this charge heterogeneity. The basis for the overall charge difference between the VP1 of 3049 virus and several other strains (lpD, lpS, ts59, and A2) was studied, using recombinant viruses constructed of specific sequences derived from 3049 and lpD genomes. The portion of the VP1 polypeptide carrying the altered charge could be mapped to the body of the molecule 3' to the HindIII site at 45.0 map units (3,918 base pairs). This clearly segregates the VP1 charge phenotype from the cyc phenotype of 3049 in which capsid proteins are overproduced and accumulate in the cytoplasm of infected cells. (Author abstract) (32 Refs)

VIRUS-ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

13. TRANSFORMATION OF HUMAN LEUKOCYTES BY COCULTIVATION WITH AN ADULT T CELL LEUKEMIA VIRUS PRODUCER CELL LINE.

Yamamoto N, Japan, Okada M, Koyanagi Y, Kannagi M, Hinuma Y
Inst. Virus Res., Kyoto Univ., Kyoto 606
Science; 217(4561):737-739 1982

The transmission of adult T cell leukemia virus, a human retrovirus, into fresh leukocytes from normal humans was examined. One of three virus-carrying cell lines, tested after being subjected to lethal x-irradiation, consistently transformed leukocytes from adult peripheral blood and umbilical cord blood. All the transformed cell lines expressed adult T cell leukemia virus-associated antigen, but transformed lines originating from adult and umbilical cord blood exhibited T cell and non-T, non-B cell surface natures, respectively. Efforts to transform human leukocytes with cell-free virus were unsuccessful. (Author abstract) (16 Refs)

14. LYMPHOCYTE RESPONSES TO HERPES SIMPLEX VIRUS ISOLATES FROM PATIENTS WITH PRIMARY AND RECURRENT HERPES SIMPLEX GENITALIS.

Reichman RC, Fisher SE, Dolin R
Infectious Diseases Unit, Univ. Vermont Coll. Medicine, Given Medical Building, Burlington, VT, 05405
Am J Med; 73(1A):86-90 1982

The ability of herpes simplex virus (HSV) isolates from patients with herpes simplex genitalis (HSG) to induce lymphocyte transformation in cells from unrelated, healthy, seropositive donors was examined in a standard lymphocyte transformation assay. All HSV isolates were obtained, before the initiation of therapy, from patients who were enrolled in a placebo-controlled trial of acyclovir in the treatment of HSG. Isolates from patients with primary infections were used, as well as those from patients with frequent (8 or more episodes per yr) or infrequent (2 or fewer per yr) recurrent disease. Blastogenic responses to isolates from patients with infrequent HSG recurrences were significantly less than those to isolates from patients with either primary infections or frequent recurrences. No differences between the latter two groups of isolates were seen. These observations demonstrate that differences among naturally occurring HSV isolates exist as determined by this in vitro assay of host-virus interactions. Differences among strains may be important in the pathogenesis of HSV infections, particularly with respect to latency. (Author abstract) (29 Refs)

15. DIMER-SIZE DNA CIRCLES IN A LEUKEMIC CELL IMMORTALIZED WITH THE EPSTEIN-BARR VIRUS.

Gussander E, Adams A
Wallenberg Lab., Univ. Uppsala, S-751 22 Uppsala, Sweden
Proc Natl Acad Sci USA; 79(15):4770-4774 1982

The intracellular state of the 30 viral genome equivalents of Epstein-Barr virus (EBV) DNA carried in latent form by the CII cell line, established from a chronic lymphocytic leukemia patient, has been partially characterized. The CII line, which has markers confirming its tumor origin, extends the analysis of the intracellular state of EBV DNA to include other, non-Burkitt lymphoid tumor cells. Monomer-size, free, circular EBV genomes, the major intracellular viral DNA species in other EBV-transformed cells, were absent or present in only minor amounts. Instead, EBV DNA sequences were found associated with a circular DNA form twice the size of the 110 x 10(6) Mr EBV genome. Though circular dimers of mtDNA have been found exclusively in human leukemic lymphocytes, the CII line is similar to normal cells in having only monomer-size mtDNA molecules, which can occur either singly or as catenated forms of two or more interlocking 5-um mtDNA circles. (Author abstract) (36 Refs)

16. BIOCHEMICAL BASIS FOR THE DIFFERENTIAL SENSITIVITY OF HUMAN T- AND B-LYMPHOCYTE LINES TO 5-FLUOROURACIL.

Piper AA, Fox RM
Ludwig Inst. for Cancer Res., Univ. Sydney, Blackburn Building, Sydney, New South Wales 2006, Australia
Cancer Res; 42(9):3753-3760 1982

The metabolism of 5-fluorouracil (FUra) was examined in two human lymphocyte cell lines, CCRF-CEM (T-leukemic) and LAZ-007 (Epstein-Barr virus-transformed B), which have widely differing FUra sensitivities. CEM cells have orotate phosphoribosyltransferase but no uridine or thymidine phosphorylase activity. Consistent with this, the FUra growth inhibition and the synthesis of fluorouridine triphosphate (FUTP) and fluorodeoxyuridine monophosphate (FdUMP) in CEM cells was substantially reduced by hypoxanthine and allopurinol. FUra growth inhibition of CEM cells was due to inhibition of both DNA and RNA synthesis, since thymidine only partially restored growth. Growth inhibition of LAZ cells, which possess all of the above FUra-activating enzymes, occurred at a lower FUra concentration than for CEM cells and was due (at FUra concentrations giving 95% growth inhibition) to inhibition of thymidylate synthesis, since thymidine completely restored growth. Consistent with this, the LAZ cells synthesize FdUMP at much higher rates than do CEM cells. FdUMP synthesis was not significantly inhibited by hypoxanthine but was activated by deoxyinosine and strongly inhibited by thymidine, leading us to conclude that LAZ cells synthesize FdUMP predominantly via thymidine phosphorylase. At higher (greater than 10(-6) M) FUra concentrations, thymidine only partially restored LAZ cell growth, indicating impairment of RNA metabolism apparently due to FUTP synthesized via orotate phosphoribosyltransferase since (a) substantial protection was obtained by addition of hypoxanthine to FUra plus thymidine and (b) FUTP synthesis in LAZ cells was strongly inhibited by hypoxanthine. Thus, the increased FUra sensitivity of LAZ cells is due primary to their greater rate of FdUMP synthesis via thymidine phosphorylase. Impairment of RNA metabolism occurred in both cell lines at similar FUra concentrations and was due to FUTP synthesis via orotate phosphoribosyltransferase, the activity of which is similar in LAZ and CEM cells. (Author abstract) (49 Refs)

17. S-ADENOSYLHOMOCYSTEINE HYDROLASE INHIBITION IN DEOXYADENOSINE-TREATED HUMAN T-LYMPHOBLASTS AND RESTING PERIPHERAL BLOOD LYMPHOCYTES.

Kefford RF, Helmer MA, Fox RM
Ludwig Inst. Cancer Res. (Sydney Branch), Univ. Sydney, Blackburn Building, New South Wales 2006, Australia
Cancer Res; 42(9):3822-3827 1982

The pattern of inhibition and recovery of intracellular S-adenosylhomocysteine hydrolase (AdoHcyase) activity induced by cytotoxic concentrations of 2'-deoxyadenosine (dAdo) in the presence of the adenosine deaminase inhibitor erythro-9-[3-(2-hydroxynonyl)]adenine was studied in cultured human T-lymphoblasts (CCRF-CEM and -HSB), Epstein-Barr virus-transformed B-lymphoblasts (JP and RDG), and resting peripheral blood lymphocytes. In the presence of 5 uM erythro-9-[3-(2-hydroxynonyl)]adenine the AdoHcyase activity was inhibited 50% after 1 hr of incubation by 3, 10, and 30 uM dAdo for B-lymphoblasts, T-lymphoblasts, and peripheral blood lymphocytes, respectively, while cytotoxicity (to 50% of controls) was effected by 600, 3, and 1 uM dAdo, respectively. Cytostatic concentrations of dAdo, which induce G1-phase arrest in T-lymphoblasts, inhibited AdoHcyase to 30% of control at 4 hr, after which recovery to normal levels occurred over 24 hr. Coincubation with 50 uM 2'-deoxycytidine, which protects these cells from both G2-phase arrest and growth inhibition by dAdo, had no effect on the pattern of inhibition of AdoHcyase activity. Epstein-Barr virus-transformed B-lymphocytes exposed to the same concentrations of dAdo were not growth inhibited but displayed patterns of AdoHcyase inhibition closely similar to those seen in T-lymphoblasts. Coincubation with 20 uM 2'-deoxycytidine, despite its protective effect against dAdo cytotoxicity, had no effect on the pattern of AdoHcyase inhibition in resting peripheral blood lymphocytes induced by 10 uM dAdo and 5 uM erythro-9-[3-(2-hydroxynonyl)]adenine over a 72-hr period. The lack of correlation between cytotoxicity and AdoHcyase inhibition in human lymphoid cells suggest that other mechanisms may account for the toxic effects of dAdo in these cells. (Author abstract) (39 Refs)

18. COMPLEMENTATION BETWEEN INFECTING EPSTEIN-BARR VIRUS AND INTRINSIC VIRAL GENOMES IN HUMAN LYMPHOID CELL LINES.

Lidin BI, Lamon EW, Cloud G, Soong SJ
(c/o Lamon) Dept. Surgery, Univ. Alabama in Birmingham, Sch. Medicine, Birmingham, AL, 35294
Intervirology; 18(1/2):66-75 1982

Thirteen human lymphoid cell lines previously characterized in terms of their intrinsic Epstein-Barr virus (EBV) genome content were infected or superinfected with EBV from the supernatant of P3HR-1 cells. The cell lines included two lymphoma cell lines that contain no detectable EBV genomes and 11 cell lines containing intrinsic EBV genomes. All the cell lines responded to EBV infection by expressing early antigen (EA). The number of EA-positive cells in the cultures was proportional to the viral concentration used for infection or superinfection. However, cell lines containing multiple intrinsic EBV genomes expressed higher amounts of EA-positive cells. Evaluation of EA expression vs the number of intrinsic EBV genome copies per cell in each cell line revealed EA to increase as the intrinsic EBV genome content of the cell lines increased in a nonlinear curve that was described by an exponential logistic function. The coefficient of determination R2 for this curve was greater than 0.9 for multiple experiments. The data suggest that 80-90% of the virus in P3HR-1 is defective and requires intrinsic viral genomes for expression of EA. Transactivation or complementation between intrinsic EBV genomes and infecting virus is supported by these observations. (Author abstract) (35 Refs)

19. CHANGES IN THE EXPRESSION OF FC RECEPTOR PRODUCED BY INDUCTION OF EPSTEIN-BARR VIRUS IN LYMPHOMA CELL LINES.

Yee C, Costa J, Hamilton V, Klein G, Rabson AS
Lab. Pathology, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD, 20205
Virology; 120(2):376-382 1982

Induction of Epstein-Barr virus (EBV) in the human lymphoma lines P3HR-1, and Daudi by TPA (phorbol-12-myristate-13-acetate), n-butyrate, and superinfection with P3HR-1 virus is associated with an increase in the number of cells bearing Fc receptor (Fc-R). The number of Fc-R per cell, as measured by flow cytometry, is also increased in both cell lines after effective induction of EBV antigens. The increase in cells bearing Fc-R correlates with increased expression of the membrane antigen complex (MA). A high proportion of induced cells concomitantly express both Fc-R and MA in double fluorescence studies. Fc-R activity was not induced by these treatments in EBV-negative lines. After induction of B-95-8 cells (an EBV transformed marmoset cell line), there is an increase both in MA and whole virus production; however, no Fc-R activity has been detected, suggesting that the B-95-8 EBV strain is incapable of inducing an Fc-R at the cell surface. (Author abstract) (20 Refs)

20. INDUCTION OF THE SYNTHESIS OF A 70,000 DALTON MAMMALIAN HEAT SHOCK PROTEIN BY THE ADENOVIRUS E1A GENE PRODUCT.

Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 29(3):913-919 1982

We have attempted to determine whether any cellular genes are activated as a result of the action of the adenoviral E1A gene. The proteins synthesized in uninfected HeLa cells have been compared to those produced in early adenovirus infected cells. At least one protein, absent from uninfected HeLa cells, was synthesized in large amounts following adenovirus infection. This 70 kd protein was not synthesized in cells infected with the E1A mutant dl312, even when the multiplicity of infection with the mutant was such that the only viral gene not expressed was the E1A gene. Thus the induction of the 70 kd protein requires the expression of the viral E1A gene. The 70 kd protein was also induced by heat shock in uninfected cells. The same 70 kd protein is synthesized in 293 cells, a line of human embryonic kidney cells transformed by a fragment of adenovirus DNA. These cells constitutively express the E1A and E1B genes. (Author abstract) (22 Refs)

21. CHARACTERIZATION OF SV40-TRANSFORMED HUMAN LIVER CELLS BEFORE AND AFTER PASSAGE THROUGH CRISIS.

Buitenwerf J, De Jong W, Van Strien A, Van der Noordaa J
(c/o van der Noordaa) Laboratorium voor de Gezondheidsleer, Universiteit van Amsterdam, Mauritskade 57, 1092 AD Amsterdam, The Netherlands
Intervirology; 17(4):222-227 1982

SV40-transformed human liver cells could be passed through crisis after transfection with various DNAs (SV40, BKV, or salmon sperm). The pre- and post-crisis cells were compared with respect to growth behavior and the state of the viral genome. Comparison of the viral inserts in the pre- and post-crisis cells showed minor changes in the integration pattern of the SV40 DNA after recovery from crisis. (Author abstract) (18 Refs)

22. 3-AMINOBENZAMIDE SYNERGISTICALLY INCREASES SISTER-CHROMATID EXCHANGES IN CELLS EXPOSED TO METHYL METHANESULFONATE BUT NOT TO ULTRAVIOLET LIGHT.

Morgan WF, Cleaver JE

Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143

Mutat Res; 104(6):361-366 1982

The effects of 3-aminobenzamide on the production of sister-chromatid exchanges induced by methyl-methanesulfonate (MMS) and UV light in Chinese hamster ovary cells (CHO) and Simian virus 40 (SV40)-transformed human cells (GM637) were investigated. Synergism between 3-aminobenzamide and MMS was observed, while no significant effect was seen with 3-aminobenzamide and UV light in either cell type. (25 Refs)

23. CHEMOTACTIC PROPERTIES AND BIOCHEMICAL FEATURES OF MALIGNANT CELLS IN VITRO (MEETING ABSTRACT).

Mensing H, Albini A, Krieg T, Muller P, Pontz B, Meigel W

University Hautklinik, 2000 Hamburg, W. Germany

J Invest Dermatol; 78(4):331 1982

The pathophysiology of expansive growth and metastasis of malignant tumors is little understood. One of the crucial features of tumor-cells is their motility and response to chemoattractants like fibronectin (FN) and collagen derived peptides (CDP). Since tumor-cells are known to have an altered synthesis of collagen and FN resulting in a reduced connective tissue matrix it was the aim of this study to investigate their chemotactic response to FN and CDP. Rhabdomyosarcoma-, fibrosarcoma-, SV 40 transformed human lung fibroblasts and 5 cell strains derived from human dermatofibrosarcoma protuberans - each characterized by the synthesis of a specific pattern of structural proteins - were grown and compared to normal human fibroblasts in respect to their synthesis of collagen, FN and their chemotactic activity. In result chemotaxis was correlated to the amounts of FN synthesis of the different cell types: Cells, producing less FN show markedly increased chemotactic migration, when FN or CDP are used as attractant. In addition less minimal concentration of attractant was necessary to stimulate chemotaxis in these cells. In contrast no alteration of chemotactic activity could be noticed in DFP cells, which show a collagen- and FN synthesis similar to that of controls. These data suggest that idea that increased chemotactic response to relatively higher levels of FN and CDP in the environment of malignant tumors play an important role in the initial metastasizing process. In addition this could also explain the predominant location of metastases in connective tissue rich organs. (no Refs)

24. EVIDENCE FOR NON-CHROMOSOMAL HEPATITIS B VIRUS SURFACE (HBSAG)- AND CORE ANTIGEN (HBCAG)-SPECIFIC DNA SEQUENCES IN A HEPATOMA CELL LINE.

Marquardt O, Zaslavsky V, Hofschneider PH
Max-Planck-Institut fur Biochemie, 8033 Martinsried, W. Germany
J Gen Virol; 61(part1):105-109 1982

As demonstrated previously, a 'beta particle' fraction isolated from the cytoplasm of PLC/PRF/5 cells contains hepatitis B virus (HBV)-specific DNA. Here, further evidence is provided that the specificity of the DNA for HBV is represented at least by sequences coding for the surface and core antigen (HBsAg and HBcAg). This was shown by two different hybridization techniques. One of them, the technique of Southern, distinguished these hybrid molecules formed from those containing HBV DNA integrated into chromosomes. The HBV-specific beta particle DNA forms two distinct bands separate from the high mol wt cellular DNA. (Author abstract) (13 Refs)

25. A NOVEL CELL TRANSFORMATION WITH DNA-CONTAINING CYTOPLASMIC YABA TUMOR POXVIRUS.

Rouhandeh H, Vafai A
Lab. Molecular and Cancer Virology, Dept. Microbiology, Southern Illinois Univ., Carbondale, IL, 62901
Virology; 120(1):77-92 1982

Monkey kidney cells were morphologically transformed in vitro with uv-irradiated Yaba tumor poxvirus. Cell lines established were shown to be virus nonproducers and exhibited biological characteristics typical of transformed cells. These characteristics included increased saturation density, reduced serum requirements for growth, and ability to grow in soft agar. The morphological alterations of transformed cells were similar to Yaba virus-induced tumor cells and were characterized by loss of contact inhibition, multinucleated cells, and cytoplasmic lipid droplets. Southern blot hybridization revealed that sequences homologous to low-mol-wt viral DNA were present in the transformed cells. Yaba virus-specific antigens detected by immunofluorescence assays were found to be in the cytoplasm of transformed cells. Four virus-specific proteins, with mol wt of 160,000, 140,000 107,000, and 74,000 daltons, were detected in transformed cells immunoprecipitated with sera from tumor-bearing monkeys. These results indicate that DNA-containing Yaba tumor virus, which replicates exclusively in the cytoplasm, is capable of inducing cell transformation in vitro. (Author abstract) (32 Refs)

VIRUS REPLICATION AND EXPRESSION

26. TRANSFECTION WITH THE PROVIRAL DNA OF A TYPE D RETROVIRUS (MASON-PFIZER MONKEY VIRUS).

Ogura H, Fujiwara T, Takechi H
Dept. Virology, Cancer Inst., Okayama Univ. Medical Sch., 2-5-1 Shikatacho, 700 Okayama, Japan
Intervirology; 18(1/2):95-97 1982

Chromosomal DNA was isolated from CMMT cells which were producing Mason-Pfizer monkey virus (M-PMV), a Type D simian retrovirus. Human embryonic cells were transfected with the DNA. About 2 wk after transfection, three of seven culture dishes began to produce M-PMV which could be detected by virus-mediated cell fusion in RSb human cells dually transformed by Rous sarcoma virus and simian virus 40, reverse transcriptase assay, and electron microscopy. Mock-transfected cultures did not produce virus. (Author abstract) (11 Refs)

27. EPSTEIN-BARR VIRUS ACTIVATION WITH EUPHORBIACEAE PLANT EXTRACTS: A POSSIBLE CAUSE FOR BURKITT'S LYMPHOMA AND NASOPHARYNGEAL CARCINOMA.

Ito Y, Yanase S, Morigaki T, Kishishita M
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Excerpta Med Int Congr Ser; 571:423-427 1982

Speculation is raised as to whether Epstein-Barr virus-activating substances generated by Fusobacterium and other anaerobes in the mouth, and diterpene esters in Euphorbiaceae extracts with similar activity, might interact in the mouth to initiate the first step of carcinogenesis, which eventually may lead to Burkitt's lymphoma. Similar chronic inflammation in the nasal cavity and nasopharynx could serve to cause nasopharyngeal carcinoma. (2 Refs)

28. ACTIVATION OF EPSTEIN-BARR VIRUS EXPRESSION IN HUMAN LYMPHOBLASTOID P3HR-1 AND RAJI CELLS WITH PROPIONIC ACID AND WITH CULTURE FLUIDS OF PROPIONIC ACID-PRODUCING ANAEROBES.

Kishishita M, Yanase S, Ito Y
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Cancer Lett; 16(2):117-120 1982

Epstein-Barr virus (EBV) expression was studied in EBV genome-carrying cells (P3HR-1 and Raji) cultured with four species of propionic acid (PA)-producing microbes (Propionibacterium acnes, Propionibacterium avidum, Propionibacterium lymphophilum, and Arachnia propionica) commonly isolated from mouth, skin, and intestinal tract of man. After 48 hr, 20-40% of the cells were EBV-early associated (EA) positive and 15-20% were virus capsid antigen positive as assayed by indirect immunofluorescence assay. EBV inducing capacity appeared to correlate with the fatty acid content in the culture fluid. PA per se was assayed for the capacity to induce EBV-associated antigens. EBV inducing activity of P3HR-1 cells was observed at PA concentrations greater than 10 mM. In non-producer Raji cells, PA combined with croton oil (CRO) or n-butyrate enhanced induction of EA. The EBV-inducing capacity of PA in non-producer Raji cells when used with CRO, a tumor promoting agent, is interesting from the point of view of skin carcinogenesis. The role of PA-producing microbes of normal cutaneous flora, P acnes in particular, in the neoplastic process is not known. (9 Refs)

29. SIMPLE ASSAY METHOD FOR SUSCEPTIBILITY OF HUMAN LYMPHOCYTES TO EPSTEIN-BARR VIRUS INFECTION.

Takada K, Osato T
(c/o Osato) Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan
Intervirology; 18(1/2):87-91 1982

On the basis of the sequential early events induced by Epstein-Barr virus (EBV), the infectability of human lymphocytes to EBV was quantified as a plateau value of the max nuclear antigen (EBNA) synthesis preceding cellular DNA synthesis. The frequency of EBV-infectable cells was an av of 7.6% of unfractionated umbilical cord lymphocytes and was 4.9% in the counterparts from human adults. In the B-cell-enriched populations, the av plateau values were 29.2% in umbilical cord and 15.5% in adult samples. This method is simple and applicable for quantitative assay of the sensitivity to EBV infection of a given lymphocyte preparation. (Author abstract) (18 Refs)

30. LACK OF DETECTABLE DNA DAMAGE IN CELLS PRODUCTIVELY INFECTED WITH HUMAN CYTOMEGALOVIRUS.

Nishiyama Y, Aoki H, Tsurumi T, Maeno K

Dept. Microbiology, Germfree Life Res. Inst., Nagoya Univ. Sch. Medicine, Showa-ku, Nagoya, Aichi 466, Japan

Microbiol Immunol; 26(5):435-439 1982

DNA damage was studied in human embryonic fibroblasts (HEF) infected with human cytomegalovirus (HCMV). HEF were mock infected or infected with HCMV or herpes simplex type 2 (HSV-2). Some cell cultures were exposed to UV radiation. DNA synthesis was detected by labeling with [3H]thymidine. DNA was analyzed by CsCl density gradient equilibrium centrifugation and alkaline sucrose gradient sedimentation. Uninfected cells exposed to 400 ergs/cubic mm immediately prior to labeling served as controls. Mock-infected cells in the presence of bromouridine (BUdR) synthesized DNA with a much higher density than labeled cellular DNA. UV-irradiated cells produced DNA with two density peaks, one corresponding to that in mock-infected cells and one corresponding to cellular DNA. In cells infected with HCMV, synthesis of viral DNA predominated 96-98 hr after infection (pi) in the absence of BUdR. In the presence of BUdR both cellular and viral DNA densities shifted to higher peaks. When labeling was performed 144-146 hr pi, viral DNA synthesis again predominated; both viral and cellular DNA were sensitive to hydroxyurea. When HCMV-infected cells were superinfected with HSV-2 in the absence of BUdR, DNA with three density peaks was produced. These peaks corresponded to cellular, HCMV, and HSV-2 DNA. Analysis of DNA indicated that HSV-2 produced strand breaks in cellular DNA, while HCMV did not. Cells productively infected with HCMV are evidently capable of repair replication even in late stages of infection. HCMV evidently does not cause damage to cellular DNA. (6 Refs)

31. SOME BIOLOGICAL PROPERTIES OF LARGE-PLAQUE CLONE 230 OF SIMIAN ADENOVIRUS SA7(C8).

Vikhnovich EM, Zolotarskaia EE, Loparev VN, Dreizin RS

D. I. Ivanovskii Inst. Virology, Moscow, USSR

Vopr Virusol; (3):365-369 1982

The results of identification and evaluation of biological properties of clone 230 of simian adenovirus SA7(C8) are reported. All tested cell lines (green monkey kidney cells, Vero, and 4647) were sensitive to the cytopathic effect of clone 230. Inoculation of hamsters with clone 230 produced tumor in 44% of the animals; av latent period of tumor development was 90 days. The oncogenicity of large-plaque clone 230 was lower than that of a small-plaque clone MB-1. (9 Refs) (In RUS)

32. TUMOR VIRUS INDUCTION AND HOST CELL CAPACITY INACTIVATION: POSSIBLE IN VITRO TESTS FOR PHOTOSENSITIZING CHEMICALS.

Bockstahler LE, Coohill TP, Lytle CD, Moore SP, Cantwell JM, Schmidt BJ

Bureau Radiological Health, Public Health Service, Food and Drug Admin., U.S. Dept. Health and Human Services, 5600 Fishers Lane (HFX-120), Rockville, MD, 20857

JNCI; 69(1):183-187 1982

The responses of two in vitro mammalian virus-host cell systems to the photosensitizing chemicals proflavine sulfate and 8-methoxypsoralen (8-MOP) in the presence of light are described. Infectious simian virus 40 (SV40) could be induced from SV40-transformed hamster cells by treatment with proflavine plus visible light or 8-MOP plus near UV radiation. The same photosensitizing treatments inactivated the capacity of monkey cells to support the growth of herpes simplex virus. SV40 induction and inactivation of host cell capacity for herpesvirus growth might be useful as screening systems for testing the photosensitizing potential of chemicals. Advantages and disadvantages associated with each system are discussed. (Author abstract) (26 Refs)

33. LABELING AND SELECTIVE RECOVERY OF NEWLY SYNTHESIZED VIRAL DNA FROM SIMIAN VIRUS 40-INFECTED CELLS INCUBATED WITH INORGANIC THIOPHOSPHATE.

Sun IY, Allfrey VG

(c/o Allfrey) Rockefeller Univ., New York, NY, 10021

Proc Natl Acad Sci USA; 79(15):4589-4593 1982

African green monkey CV-1 cells infected with simian virus 40 (SV40) were incubated in the presence of sodium [35S]thiophosphate. The viral DNA was prepared and the newly synthesized SV40 DNA molecules containing phosphorothioate groups were selectively recovered by affinity chromatography on organomercurial-Sepharose columns. The thioderivatized viral DNA occurred in both superhelical (Form I) and relaxed circular (Form II) configurations, and it gave the expected cleavage products upon digestion with the restriction endonucleases Kpn I and HindIII. Enzymatic digestion of 35S-labeled SV40 DNA to its component nucleotides and chromatographic separation of the resultant 5'-labeled phosphorothioate esters established the presence of the label in all four major nucleotides, but mainly in thymidylic acid. The ability to label and recover selectively the newly synthesized polynucleotides by incubating cells with inorganic thiophosphate complements earlier findings that thiophosphate enters intracellular nucleotide pools and serves as an effective precursor for the phosphorylation of nuclear proteins in vivo. (Author abstract) (33 Refs)

VIRAL GENETICS AND MOLECULAR BIOLOGY

34. T24 HUMAN BLADDER CARCINOMA ONCOGENE IS AN ACTIVATED FORM OF THE NORMAL HUMAN HOMOLOGUE OF BALB- AND HARVEY-MSV TRANSFORMING GENES.

Santos E, Tronick SR, Aaronson SA, Pulciani S, Barbacid M
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 298(5872):343-347 1982

A transforming gene isolated from T24 human bladder carcinoma cells is closely related to the BALB murine sarcoma virus (MSV) onc gene (v-bas). This transforming gene is localized to a 4.6 kilobase pair (kbp) region and is expressed as a 1.2-kbp polyadenylated transcript, which contains v-bas related sequences. Moreover, antisera known to detect the immunologically related onc gene products of BALB- and Harvey-MSV recognized elevated levels of a related protein in T24 cells. The normal human homologue of v-bas was found to be indistinguishable from the T24 oncogene by heteroduplex and restriction enzyme analysis. These results imply that rather subtle genetic alterations have led to the activation of the normal human homologue of v-bas as a human transforming gene. (Author abstract) (48 Refs)

35. CHROMOSOMAL ASSIGNMENT OF THE HUMAN HOMOLOGUES OF FELINE SARCOMA VIRUS AND AVIAN MYELOBLASTOSIS VIRUS ONC GENES.

Dalla-Favera R, Franchini G, Martinotti S, Wong-Staal F, Gallo RC, Croce CM
Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(15):4714-4717 1982

Retroviral transforming genes, v-onc genes, are derived from normal cellular sequences that are called cellular onc (c-onc) genes. DNA from mouse-human somatic cell hybrids that have selectively lost human chromosomes was used in Southern blots to map the chromosomal location of two human onc genes. Cloned human homologues of retroviral onc genes were used as probes. Because the human c-fes gene, which is homologous to feline sarcoma virus, segregates concordantly with human chromosome 15, and the human c-myb gene, which is homologous to avian myeloblastosis virus onc genes, segregates concordantly with human chromosome 6, we have assigned the c-fes and the c-myb genes to human chromosomes 15 and 6, respectively. Nonrandom chromosomal defects involving these human chromosomes have been observed in neoplasms. These studies should be valuable in determining whether specific rearrangements involving these chromosomes result in the abnormal expression of these onc genes in human malignancies. (Author abstract) (45 Refs)

36. CLONED ENDOGENOUS RETROVIRAL SEQUENCES FROM HUMAN DNA.

Bonner TI, O'Connell C, Cohen M
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Proc Natl Acad Sci USA; 79(15):4709-4713 1982

We have screened a human DNA library using as probe a chimpanzee sequence that contains homology to the polymerase gene of the endogenous baboon virus. One set of overlapping clones spans about 20 kilobases and contains regions of DNA sequence homology to the gag p30, gag p15, and polymerase genes of Moloney murine leukemia virus. Furthermore, the spacings are the same as in Moloney virus between these sequences and a 480-nucleotide region that has the structural characteristics of a 3' copy of the long terminal repeat sequence. Hybridization of the cloned DNA to restriction digests of human DNA indicates that the human genome contains only 2 copies closely related to the sequence and approx 10 less closely related copies. This retroviral sequence appears to have been in its present chromosomal location prior to the divergence of man and chimpanzee because the human and chimpanzee clones have 3-4 kilobases of identical 3' flanking sequence. (Author abstract) (27 Refs)

37. TRANSFECTION WITH THE ISOLATED HERPES SIMPLEX VIRUS THYMIDINE KINASE GENES. II. EVIDENCE FOR AMPLIFICATION OF VIRAL AND ADJACENT CELLULAR DNA SEQUENCES.

Reyes GR, McLane MW, Hayward GS
Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, 725 North Wolfe St., Baltimore, MD, 21205
J Gen Virol; 60(part2):209-224 1982

We have previously described several series of biochemical transformation experiments in which small defined portions of herpes simplex virus (HSV-1 and HSV-2) DNA encompassing the thymidine kinase (TK) gene were introduced into Ltk- cells by the calcium transfection procedure. The presence of authentic virus TK enzyme in several subcloned cell lines derived from these experiments was confirmed by either the specific incorporation of [125I]iododeoxycytidine into their nuclei or the inhibition of cell growth by the antiviral drug arabinosyl thymine. A panel of 24 independent Ltk+ cell lines receiving either isolated virus DNA fragments or cleaved plasmid DNAs was examined by blot hybridization for both the presence and copy number of virus TK DNA sequences. Most cell lines contained a single virus DNA fragment covalently joined to host (or carrier Ltk(-)) mouse DNA sequences, but several contained multiple copies of the TK gene. Examination of the structural arrangement of the virus DNA in two early passage multicopy cell lines indicated that the TK gene had integrated into Ltk- cell DNA and then subsequently both viral and flanking cellular sequences were amplified to create up to 20 tandem duplications. In one case, mapping of the adjacent cellular sequences has revealed that the total repeat unit is greater than 23 kilobases (kb) in size. On subsequent passaging, even in HAT medium, the amplified repeat units were not stable and fell to only three to four copies per haploid cell genome. These cell lines should prove useful for additional studies to examine the expression of co-selected non-TK virus sequences and the influence of adjacent cellular DNA sequences on transcription and retransfection of the resident TK gene. (Author abstract) (45 Refs)

38. MOLECULAR STRUCTURE OF HERPESVIRUS PAPIO DNA AND CLONING OF ITS REPEAT SEQUENCE IN PLASMID PACYC 184.

Lee YS, Nonoyama M, Rabin H
Showa Univ. Res. Inst. for Biomedicine in Florida, 5180 113th Ave. North, Clearwater, FL, 33520
Excerpta Med Int Congr Ser; 571:12-18 1982

Genetic engineering technology was used to analyze the genomes of herpes virus Papio (HVP) DNA. HVP productive cells (594S/F9) were propagated at 37 C. Virus was isolated from productive cells treated with 12-O-tetradecanoylphorbol-13-acetate. Blotting hybridization and double enzyme digestion was used to form an overall linkage map of HVP DNA. Similarity was found between HVP and Epstein-Barr virus (EBV) in both biological and biochemical aspects. Terminal heterogeneity and internal repeat sequence (IR) were unique features in EBV and HVP DNA and was also found in gorilla DNA isolated from a productive lymphoblastoid cell line. It is suggested that IR might be a unique sequence among all primate EBV-like viruses. (15 Refs)

39. THE DETECTION AND MAPPING OF CONSERVED NUCLEOTIDE SEQUENCES BETWEEN THE GENOMES OF HUMAN PAPILLOMAVIRUS 1A AND BOVINE PAPILLOMAVIRUS 1 BY ELECTRON MICROSCOPE HETERODUPLEX ANALYSIS.

Croissant O, Testamiere V, Orth G

Unite des Papillomavirus, Institut-Pasteur, 25, rue du Docteur Roux, 75724 Paris, France

C R Seances Acad Sci [III]; 294(12):581-586 1982

The genome of papillomavirus (PV) is formed of about 8000 base pairs. In natural conditions, PV may cause epithelial or benign fibroepithelial tumors of the skin or mucosa which in certain cases can evolve toward malignancy. The virus only reproduces in keratinocytes in benign tumors. A fragment representing only 69% of the genome is required for PV transformation by bovine PV 1 (BPV 1). Electron microscope analysis of heteroduplex molecules revealed three regions of partial homology between the genomes of human papillomavirus 1a and BPV1. These regions represent about 25% of non-homologous bases and 13% of the genome length. The regions were mapped on viral DNA which allowed a reciprocal orientation of the physical maps of the two genomes. Two regions were located in the middle of the transforming fragment of BPV-1 DNA and the third region, which was located in an entirely different area, was in the region of the genome coding that was probably for a viral structural protein. (19 Refs) (In FRE)

40. DIFFERENTIAL COMPLEMENTATION OF ADENOVIRUS TYPE 5 TEMPERATURE-SENSITIVE EARLY MUTANTS BY ADENOVIRUS TYPES 3 AND 12.

McDonough JS, Rekosh DM

(c/o Rekosh) Dept. Biochemistry, State Univ. New York at Buffalo, Buffalo, NY, 14214

Virology; 120(2):383-398 1982

We have assayed the ability of human adenoviruses from heterologous subgroups to complement early temperature-sensitive mutants of the C group virus Ad5 by analyzing coinfections at the restrictive temperature for serotype-specific DNA and late protein synthesis. Our results indicate that the B group virus Ad3, does not complement either ts125 or the N complementation group of Ad5 (ts36, ts69, and ts149). In contrast, studies with Ad12, an A group virus, and these mutants, indicate a differential complementation in that Ad12 complements all of the mutants in the Ad5 N complementation group but does not complement ts125. Failure to complement the ts125 defect in coinfected cells has been shown to be due to the inability of the heterologous wt gene product to substitute for the ts125 gene product directly at the level of DNA replication and not at some earlier event in the virus growth cycle. (Author abstract) (45 Refs)

41. CLONING OF DNA FRAGMENTS FROM THE LEFT END OF THE ADENOVIRUS TYPE 12 GENOME: TRANSFORMATION BY CLONED EARLY REGION 1.

Byrd PJ, Chia W, Rigby PW, Gallimore PH

Dept. Cancer Studies, Univ. Birmingham Medical Sch., Cancer Res. Campaign Lab., Birmingham B15 2TJ, England

J Gen Virol; 60(part2):279-293 1982

The human adenovirus serotype 12 (Ad-12) EcoRI-C DNA fragment (0 to 16.5 map units) was cloned in the plasmid vector pAT153. This cloned Ad-12 EcoRI-C DNA fragment was subcloned generating recombinant plasmids which contained the Ad-12 SalI-C fragment (0 to 10.3 map units), the Ad-12 HindIII-G fragment (0 to 6.8 map units) and the Ad-12 AccI-H fragment (0 to 4.7 map units). Thus, we constructed recombinant plasmids which contain Ad-12 DNA sequences which represent all or part of the virus transforming gene region. The capacity of the cloned Ad-12 EcoRI-C DNA fragment to transform rat cells in vitro was assessed using the focus assay on primary cultures of rat cells. The specific transforming activity of this recombinant plasmid was in the same range as that found for intact Ad-12 DNA. Transformed foci which were induced by the cloned Ad-12 EcoRI-C DNA fragment were established as cell lines and the presence of AD-12 DNA in these lines was demonstrated using the Southern blotting technique. (Author abstract) (47 Refs)

42. FORMATION OF A NUCLEOSOME-FREE REGION IN SV40 MINICHROMOSOMES IS DEPENDENT UPON A RESTRICTED SEGMENT OF DNA.

Jakobovits EB, Bratosin S, Aloni Y

(c/o Aloni) Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel

Virology; 120(2):340-348 1982

We have analyzed minichromosomes of SV40 mutants with the electron microscope. In two insertion mutants, containing the SV40 DNA fragment from 0.66 to 0.715 map unit duplicated diametrically opposite to its original site in two alternative orientations, one nucleosome-free region ('gap') was visualized in 25% of the molecules of each mutant with equal frequency either at the original position or at the insertion point. In a host-substituted mutant (F161F), where the viral DNA sequences spanning 0.67-0.73 map unit are interspersed as four copies between cellular sequences, one gap was visualized in almost 100% of the molecules in the vicinity of the viral DNA sequences. These observations indicate that gap formation is dependent upon SV40 DNA sequences located between 0.67 and 0.715 map unit. (Author abstract) (56 Refs)

43. STIMULATION OF HOST CENTRIOLAR ANTIGEN IN TC7 CELLS BY SIMIAN VIRUS 40: REQUIREMENT FOR RNA AND PROTEIN SYNTHESES AND AN INTACT SIMIAN VIRUS 40 SMALL-T GENE FUNCTION.

Shyamala M, Atcheson CL, Kasamatsu H

(c/o Kasamatsu) Dept. Biology and Molecular Biology Inst., Univ. California, Los Angeles, CA, 90024

J Virol; 43(2):721-729 1982

Simian virus 40 (SV40) stimulated a host cell antigen in the centriolar region after infection of African green monkey kidney (AGMK) cells. The addition of puromycin and actinomycin D to cells infected with SV40 within 5 hr after infection inhibited the stimulation of the host cell antigen, indicating that de novo protein and RNA syntheses that occurred within the first 5 hr after infection were essential for the stimulation.

Early viable deletion mutants of SV40 with deletions mapping between 0.54 and 0.59 map units on the SV40 genome, dl2000, dl2001, dl2003, dl2004, dl2005, dl2006, and dl2007, did not stimulate the centriolar antigen above the level of uninfected cells. This indicated that an intact, functional small-t protein was essential for the SV40-mediated stimulation of the host cell antigen. Our studies, using cells infected with nondefective adenovirus-SV40 hybrid viruses that lack the small-t gene region of SV40 (Ad2+ND1, Ad2+ND2, Ad2+ND3, Ad2+ND4, and Ad2+ND5), revealed that the lack of small-t gene function of SV40 could be complemented by a gene function of the adenovirus-SV40 hybrid viruses for the centriolar antigen stimulation. Thus, adenovirus 2 has a gene(s) that is analogous to the small-t gene of SV40 for the stimulation of the host cell antigen in AGMK cells. (Author abstract) (57 Refs)

44. CONSTRUCTION AND CHARACTERIZATION OF VIABLE DELETION MUTANTS OF SIMIAN VIRUS 40 LACKING SEQUENCES NEAR THE 3' END OF THE EARLY REGION.

Polvino-Bodnar M, Cole CN
Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Virol; 43(2):489-502 1982

Five viable deletion mutants of simian virus 40 (SV40) were prepared and characterized. These mutants lack 15 to 60 base pairs between map positions 0.198 and 0.218, near the 3' end of the early region of SV40 and extend further into the body of the A gene, encoding the large T antigen, than previously described deletion mutants. These mutants were isolated after transfection of monkey kidney CV-1p cells with full-sized linear DNA prepared by partial digestion of form I SV40 DNA with restriction endonucleases HinfI or MboII, followed by removal of approximately 25 base pairs of DNA from the 5' termini using gamma-5'-exonuclease and purification of the DNA in agarose gels. Based on comparisons of the DNA sequence of SV40 and polyoma virus, these mutations map in the 19% of the SV40 A gene that shares no homology with the A gene of polyoma virus. The mutations exist in two different genetic backgrounds: the original set of mutants (dl2401 through dl2405) was prepared, using as a parent SV40 mutant dl862, which has a deletion at the single HpaII site (0.725 map unit). A second set (dl2491 through dl2495) contains the same deletions in a wild-type SV40 (strain SV-S) background. Relative to wild-type SV40, the original mutants showed reduced rates of growth, lower yields of progeny virus and viral DNA, and smaller plaque size; in these properties the mutants resembled parental dl862, although mutant progeny yields were usually lower than yields of dl862, suggesting a possible interaction between the two deletions. The second set of mutants had growth properties and progeny yields similar to those of wild-type SV40; however, Southern blotting experiments indicated that viral DNA replication proceeds at a slightly reduced rate. All of the mutants transformed mouse NIH/3T3 cells and mouse embryo fibroblasts at the same frequency as wild-type SV40. Mutants dl2402, dl2492, and dl2405 consistently produced denser and larger foci in both types of cells. All mutants directed the synthesis of shortened large T antigens. Adenovirus helper function was retained by all mutants. (Author abstract) (83 Refs)

45. BIOCHEMICAL CHARACTERIZATION OF TWO TYPES OF HUMAN PAPILLOMAVIRUSES ASSOCIATED WITH EPIDERMODYSPLASIA VERRUCIFORMIS.

Kremsdorf D, Jablonska S, Favre M, Orth G
(c/o Orth) Unite INSERM 190, Institut Pasteur, 75015 Paris, France
J Virol; 43(2):436-447 1982

The DNAs of the human papillomaviruses (HPVs) associated with the benign lesions of two patients suffering from epidermodysplasia verruciformis (patients JD and JK) were analyzed by using 12 restriction endonucleases. None of the restriction endonucleases were one-cut enzymes for the HPV DNA obtained from patient JD, referred to as the prototypical HPV-5, whereas five of them were one-cut enzymes for the DNA of the major virus found in patient JK, referred to as HPV-9. The molecular cloning of the two fragments resulting from the cleavage of HPV-5 DNA by endonuclease HindIII and of the single fragment obtained after treatment of HPV-9 DNA with endonuclease BamHI was performed in Escherichia coli after the fragments were inserted in plasmid pBR322. A cleavage map of the two cloned genomes was constructed. Little sequence homology (4 to 5%) was detected between HPV-5 and HPV-9 DNAs by DNA-DNA hybridization experiments in liquid phase at saturation; this homology was reproducibly higher than that (2 to 3%) detected under the same conditions between these DNAs and HPV-1a DNA. In addition, blot hybridization experiments performed under stringent conditions showed no or little sequence homology between the DNAs of HPV-5 and HPV-9 and those of HPV prototypes of types 1,2,3,4, and 7 associated with skin warts. These results confirm that HPV-5 and HPV-9 are two distinct HPV types. (Author abstract) (44 Refs)

IMMUNOLOGICAL STUDIES

46. INHIBITORS OF MONOCYTE RESPONSES TO CHEMOTAXINS ARE ASSOCIATED WITH HUMAN NEOPLASMS (MEETING ABSTRACT).

Synderman B, Cianciolo G
Howard Hughes Medical Institute, Duke University, Durham, NC
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

We examined the effects of cancerous effusions on a newly developed assay of monocyte function. This assay quantifies monocyte polarization, ie, the rapid alteration in the cell's morphology from round to a triangular 'motile' configuration in response to chemoattractants. All 17 malignant effusions tested, representing 15 tumor types, inhibited monocyte polarization induced by the chemoattractant N-formyl-methionyl-leucyl-phenylalanine by 45-89% in binded assays. None of 17 benign effusions significantly inhibited polarization (0-15%). Dilutions of cancerous effusions as low as 1:200 produced inhibition that was time, temperature, and dose dependent. Monocyte polarization induced by activated serum or by chemotactic lymphokine was also blocked by cancerous effusions. The inhibitory activity affected the monocyte directly, and did not destroy the chemoattractant. In contrast to its effects on monocytes, the inhibitors in cancerous effusions did not affect the polarization of granulocytes to chemotactic factors. High pressure liquid chromatography of five cancerous fluids revealed three peaks of monocyte inhibitory activity: greater than or equal to 200,000, 46,000, and 21,000 daltons. Fractionation of noncancerous effusions disclosed only small amounts of the highest molecular weight inhibitory activity. The inhibitory activity in cancerous effusions was heat stable (56C, 30 min), trypsin sensitive, and could be absorbed by three different monoclonal antibodies reactive to P15(E), a structural component of oncogenic type C retroviruses. In contrast, six monoclonal antibodies with other specificities had no effect on the inhibitors or polarization. Human cancerous effusions thus contain novel proteins that are potent inhibitors of monocyte function. (no Refs)

47. EXPRESSION OF HERPES SIMPLEX VIRUS TYPE 2 ANTIGENS IN PREMALIGNANT AND MALIGNANT HUMAN VULVAR CELLS.

Cabral GA, Marciano-Cabral F, Fry D, Lumpkin CK, Mercer L, Goplerud D
Dept. Microbiology, Medical Coll. Virginia, Virginia Commonwealth Univ., Box 678-MCV Station, Richmond, VA, 23298
Am J Obstet Gynecol; 143(6):611-619 1982

Vulvar biopsies and explants from patients with vulvitis, hyperkeratosis, condyloma acuminatum, severe dysplasia, and squamous cell carcinoma were screened for herpes simplex virus Type 2 (HSV-2) antigens. Immunoperoxidase staining for VP143, an early nonstructural polypeptide of HSV-2, was identified within three biopsies exhibiting severe dysplasia, three of seven with carcinoma in situ, and one of three with invasive squamous cell carcinoma. Similar staining for VP143 was observed in derived explants. Staining for VP119, the major envelope glycoproteins of HSV-2, was identified within tissues which were positive for VP143. Both proteins were expressed in the absence of staining for virus capsid proteins, detection of virus structures by electron microscopy, and isolation of infectious virus by co-cultivation, indicating that only a fragment of the virus genome was expressed. Neither VP143 nor VP119 was identified in biopsies exhibiting vulvitis, hyperkeratosis, or condyloma acuminatum. These data indicate a close relationship between HSV-2 and vulvar neoplasia. (Author abstract) (19 Refs)

48. HUMORAL IMMUNITY AGAINST HERPES SIMPLEX VIRUS TYPE 2 IN PATIENTS WITH CERVIX CANCER.

Posevaia TA, Barinskii IF, Grigor'ev VV, Shuvaeva NI
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (3):328-330 1982

To evaluate a possible etiological relation between herpes genitalis (HG) and cervix cancer (CC), the titers of antibodies against herpes simplex virus Type 2 (HSV-2) were determined in 23 patients with cervical dysplasia, 18 patients with intraepithelial carcinoma, 60 patients with Stage I-III CC, and 20 patients with recurrent HG. Complement fixation test showed antibodies against HSV-2 in 78.3% of the patients with cervical dysplasia, 66.6% of the patients with carcinoma in situ, 88.3% of the patients with CC, and in 91.7% of the patients with HG. The incidence of HSV-2 antibodies in the neutralization test was 95.6%, 94.4%, 100%, and 100%, respectively. The antibody titers in CC patients ranged from 1:20 to 1:320 in complement fixation test and from 1:32 to 1:512 in neutralization test. These findings indicate that the women with chronic HG are at risk for CC. (5 Refs) (In RUS)

49. STUDIES OF THE CELL LINEAGE OF THE EFFECTOR CELLS THAT SPONTANEOUSLY LYSE HSV-1 INFECTED FIBROBLASTS (NK(HSV-1)).

Lopez C, Kirkpatrick D, Fitzgerald PA, Ching CY, Pahwa RN, Good RA, Smithwick EM
Sloan-Kettering Inst. for Cancer Res., 1275 York Ave., New York, NY, 10021
J Immunol; 129(2):824-828 1982

Natural killer cells that lyse herpes simplex virus-type 1-infected fibroblasts (NK(HSV-1)) have been under study because they are thought to play an important role in host defense against herpesvirus infections. Studies were undertaken of certain patient groups in order to help characterize these cells and develop evidence about the cell lineage to which these effector cells belong. Our studies of bone marrow transplant recipients indicate that this function is derived from bone marrow stem cells. NK(HSV-1) was also found to be dependent on a normal bone marrow, because patients with juvenile osteopetrosis had very low responses. Further, 15 of 17 patients with aplastic anemia (AA) and complete marrow failure also showed very low NK(HSV-1) responses, whereas 9 of 11 AA patients with some evidence of bone marrow precursors had normal responses. Our studies indicate that the NK(HSV-1) effector cells do not belong to the lymphoid lineage of hemopoietic cells. In addition, two severe combined immunodeficiency disease (SCID) patients demonstrated NK(HSV-1) responses without evidence of pre-T cells in their marrow, indicating that these effectors are not pre-T cells. Studies of patients with monocyte/granulocyte lineage dysfunctions were less conclusive. Patients with chronic granulomatous disease and certain SCID patients had normal NK(HSV-1) in spite of dysfunctions of the monocyte/granulocyte series. Although NK(HSV-1) effectors may be related to the precursors of the monocyte/granulocyte series, it is equally possible that these cells belong to an independent hemopoietic cell lineage. (35 Refs)

50. ROLE OF INTERFERON IN NATURAL KILL OF HSV-1-INFECTED FIBROBLASTS.

Fitzgerald PA, Von Wussow P, Lopez C
Sloan-Kettering Inst. Cancer Res., 425 E. 68th St., New York, NY, 10021
J Immunol; 129(2):819-823 1982

The production of interferon during natural killer (NK) assays against HSV-1-infected fibroblasts (NK(HSV-1)) was studied to determine whether this interferon was responsible for inducing the preferential lysis of herpes-virus-infected target cells over uninfected target cells. The interferon produced during NK(HSV-1) assays was analyzed and found to have the properties of HU-IFN-alpha. Little or no IFN was produced during NK assays against uninfected fibroblasts (NK(FS)) or K562 (NK(K562)) cells. Although the appearance of interferon in the culture supernatants seemed to parallel the development of cytotoxicity during NK(HSV-1) assays, the levels of cytotoxicity and IFN generated did not correlate, arguing against a strict quantitative dependence of cytotoxicity upon IFN production. NK(K562) and NK(FS) cytotoxicity developed with little or no production of IFN. When IFN-pretreated effector cells were used, there was still a preferential lysis of infected over uninfected target cells. This preferential lysis by IFN-treated effector cells of infected over uninfected targets was seen as early as 2 hr into the assay. Anti-IFN antibodies added to the NK assays, although neutralizing all the IFN produced during the assays, had no effect on NK(FS) or NK(K562) cytotoxic activity and caused a slight reduction of NK(HSV-1) activity only in one of three experiments. We conclude that although IFN is generated during NK(HSV-1) assays, this IFN cannot solely account for the increased lysis of infected over uninfected cells and that NK(HSV-1) activity is in some other way dependent on the virus infection. (Author abstract) (34 Refs)

51. A PRELIMINARY STUDY ON THE ANTI-EBV-SPECIFIC DNASE ACTIVITIES OF NASOPHARYNGEAL CARCINOMA (NPC) PATIENTS' SERA.

Pan Q, Huang D, Luo W, Jiao X, Chen J, Chen L
Cancer Inst., Zhogshan Medical Coll., Dongfeng Road IV, Guangzhou, People's Republic of China
Excerpta Med Int Congr Ser; 571:418-422 1982

An anti-DNase activity was demonstrated in the sera of patients in various stages of nasopharyngeal cancer (NPC). A combination of n-butyric acid (4 milliM) and croton oil (400 nanog/ml) was used to induce Epstein-Barr virus (EBV)-specific DNase in EBV-genome-containing cell lines Raji and PeHR-1. An assay utilizing 14C-DNA was devised to determine the effect of NPC patients' sera on the DNase activity of the cell homogenate. Because of the presence of an antibody in the sera of NPC patients, and the neutralizing effect of this antibody to the enzyme, addition of patients' sera markedly decreased the DNase activities to give anti-enzyme rates of 52-55%. The level of serum anti-enzyme activity varied from NPC patient to patient. There appeared to be a good parallelism between the anti-enzyme activity of the serum and its titer to viral capsid antigen to IgA. Further studies are in progress to confirm the practical value of this enzymological test for early detection of NPC. (5 Refs)

52. SEROLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA AND CERVICAL CANCER IN CHINA.

Zeng Y
Inst. Virology, Chinese Acad. Medical Sciences, 100 Ying Xing Jie, Xuan Wu Qu, Beijing, 100052, People's Republic of China
Excerpta Med Int Congr Ser; 571:380-388 1982

A serological study on Epstein-Barr virus (EBV) infection was performed in areas of high and low risk for nasopharyngeal cancer (NPC). A micro-complement fixation test for antibody to EBV in sera of 2,300 normal individuals of all ages indicated a positive reaction in 90-100% of children aged 3-5 yr. The geometric mean titer (GMT) from the healthy population over age 20 was significantly higher in areas of high NPC risk. This type of variation may reflect reactivation of EBV in people living in the NPC high risk area and which might be related to the occurrence of NPC. Results of serologic mass surveys of NPC are reported in Zangwu county in 1978-1980. The incidence of antibody to herpes simplex virus (HSV) 1 and 2 was determined in normal women in both a high- (Jienan county) and a low-risk (Beijing) area for cervical cancer and in patients. There was no marked difference in frequency of antibody to HSV-1 in the cervical cancer patients and in the controls from high and low risk areas. However, in the cervical cancer group, the GMT of antibody to HSV-1 was a little higher than that in the control group; this may be due to cross-reaction to antigen between HSV-1 and HSV-2. A study of age-specific incidence of HSV infection in areas of high and low cervical cancer risk indicates a relationship between early and severe infection of HSV-2 and high risk of cervical cancer. While the age-specific incidence of HSV-2 infection in China is similar to that in some western countries, the social system and life-style are quite different, indicating some other mode of infection than venereal transmission. (22 Refs)

53. NASOPHARYNGEAL CARCINOMA AND CERVICAL CARCINOMA IN TAIWAN, CHINA.

Lin TM
Natl. Taiwan Univ. Coll. Medicine, Inst. Public Health, 9 Chungshan South Road, Taipei, Taiwan, Republic of China
Excerpta Med Int Congr Ser; 571:398-407 1982

Some epidemiological studies on nasopharyngeal cancer (NPC) and cervical cancer (CC) in Taiwan are presented; possible association with oncogenic viruses is also discussed. Epidemiological data presented are based on surveys since neoplasms are not reportable in Taiwan. The age-standardized death rate (per 100,000 of population) for NPC in 1979 was 3.3 (4.6 for males, 1.9 for females). As in other countries, the rate was higher in the Chinese population. The death rate has increased slightly during the past 15 yr. Morbidity incidence from 1969-1971 of NPC was estimated at 5.4. Patients with NPC show a significantly higher anti-virus capsid antigen (VCA) titer than neighborhood controls, their families, and NPC family members. A synergistic interaction with NPC was found between all pairs of factors of smoking, ventilation, nasal balsam or oil, herb drugs, and anti-VCA titer, except that between herb drugs and ventilation. The age standardized death rate (per 100,000 of female population) for CC in 1979 was 6.9, which ranked CC fourth among causes of death in females. The death rate due to CC increased markedly after age 40 yr. CC death rates were higher in those who were ever married, compared with those who were single, widowed, or divorced. (6 Refs)

54. IMMUNOLOGY AND DIAGNOSIS OF NASOPHARYNGEAL CARCINOMA.

Ho JH, Lau WH, Kwan HC, Chan CL, Au GH, Saw D
Medical and Health Dept., Inst. Radiology, Queen Elizabeth Hosp., Wyley Road, Kowloon, Hong Kong
Excerpta Med Int Congr Ser; 571:389-397 1982

Results of a series of studies are discussed to assess the value of testing for some Epstein-Barr virus (EBV)-specific serologic and immunologic markers in the diagnosis of nasopharyngeal cancer (NPC). All the sera tested were from Chinese patients and residents in Hong Kong. The sera were titrated for IgA and IgG antibodies to viral capsid antigen (VCA) and early antigen (EA) of EBV by the indirect immunofluorescent technique. The first study showed that NPC patients have a broader spectrum and higher geometric mean titer (GMT) of serum antibodies to EBV-specific antigens than do patients with other tumors of the respiratory and upper aerodigestive tracts and healthy subjects. A second study established that there was a stepwise rise in the GMT for all four antibodies with advancing stages of disease (I-IV). A further study was done to assess the value of titration of the four antibodies in the diagnosis of NPC. IgA to VCA had the highest sensitivity with a detection rate of 95% and relatively high specificity. IgA to EA was highly specific with no false positives but a detection rate of only 78%. IgG to VCA was the least discriminatory, while EgG to EA fell between IgA to EA and IgG to VCA. An ongoing study involves the evaluation of the titration of serum IgA to VCA as a screening test for NPC in its early presymptomatic stage in subjects known to have a high risk of the disease, namely, close blood-linked relatives of Chinese NPC patients. In these patients, if the serology is suggestive, multiple nasopharyngeal biopsies are indicated. Data are presented on serum EBV-specific antibody titers in four siblings initially and at time of diagnosis of NPC. (17 Refs)

55. SEROLOGIC TESTS FOR NASOPHARYNGEAL CARCINOMA IN NORTH AMERICAN PATIENTS.

Neel HB, Pearson GR, Weiland LH, Taylor WF
Mayo Clinic and Foundation, Rochester, MN
Excerpta Med Int Congr Ser; 582:111-114 1982

The clinical value of serum titers of various Epstein-Barr virus (EBV) related antibodies was investigated in 92 North American patients with primary nasopharyngeal carcinoma (NPC), 149 patients with head and neck cancer (HNC) other than nasopharyngeal, 342 patients with benign diseases (BD) commonly seen in large otolaryngologic practices, and 100 healthy blood donors. Antibody titers of sera from patients with untreated NPC differed significantly from those of the other groups. Positive titers for the IgA anti-viral capsid antigen were found in 70% of NPC patients, only 5% of those with HNC, and 10% of those with BD. Undifferentiated and nonkeratinizing carcinomas consistently exhibited elevated antibody titers directed against viral capsid antigen and early antigen. The incidence of elevated titers was lower in patients with keratinizing squamous cell carcinoma compared with the other groups. The incidence of positive IgA anti-viral capsid antigen titers in undifferentiated and nonkeratinizing varieties were much greater than those in keratinizing squamous cell varieties. A trend toward higher antibody titers with the development of metastases was seen. Of the 13 patients who died, 8 had low antibody-dependent cellular cytotoxicity titers at diagnosis and 4 had high titers. In general, patients with very high antibody-dependent cellular cytotoxicity titers remained free of disease for as long as 4 yr; these patients should be followed closely in order to determine the prognostic value of the EBV markers. (5 Refs)

56. HUMORAL IMMUNE RESPONSE IN EPSTEIN-BARR VIRUS INFECTIONS. I. ELEVATED SERUM CONCENTRATION OF THE IGG1 SUBCLASS IN INFECTIOUS MONONUCLEOSIS AND NASOPHARYNGEAL CARCINOMA.

Kaschka WP, Hilgers R, Skvaril F
Dept. Neurology, Univ. Erlangen-Nurnberg, Schwabachanlage 6, D-8520 Erlangen, W. Germany
Clin Exp Immunol; 49(1):149-156 1982

Using radial immunodiffusion we measured IgG subclass concentrations and studied their distribution in serum samples from patients with infectious mononucleosis (IM) and nasopharyngeal carcinoma (NPC), two Epstein-Barr virus (EBV)-associated diseases, in comparison with two control groups [completely anti-EBV negative persons and subjects carrying antibodies to the viral capsid antigen (VCA)]. Antibody titers to VCA and to the early antigen (EA) were determined by indirect immunofluorescence and revealed characteristic patterns for the respective diagnostic groups. Nephelometric assays served for quantitating total protein, albumin, total IgG, IgA and IgM in all the sera. In the IM and NPC groups the concentration of IgG1 was significantly elevated by more than 50% whereas the other three subclasses remained unchanged as compared with the controls. Correspondingly, we found a significant increase of total IgG in IM and NPC. In IM, the only disease where VCA-specific IgM antibodies have been reported to occur, IgM leveles were markedly elevated. Our data suggest that the IgG1 subclass plays an important role in the humoral immune response to EBV-determined antigens and that it is possibly involved in the control of virus infection. (Author abstract) (24 Refs)

57. CRYOPRESERVATION OF HUMAN PERIPHERAL BLOOD LYMPHOID CELLS REACTIVE TO ALLOGENEIC ANTIGENS, VIRUS-TRANSFORMED AUTOLOGOUS CELLS AND AUTOLOGOUS LEUKEMIA CELLS IN IN VITRO SENSITIZATION.

Yamada H, Kodera Y, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nagoya J Med Sci; 44(3/4):117-131 1982

The ability of cryopreserved human peripheral blood lymphocytes (PBLs) to respond to Epstein-Barr virus (EBV)-transformed autologous cells, autologous leukemia cells, and allogeneic lymphocytes was studied with the use of a micro method for determination of in vitro sensitization which allows serial dilution of the responding cells. The 51Cr release assay was used to determine cell-mediated cytotoxicity. After 7 days in vitro sensitization with alloantigens, maximal cytotoxicity was obtained at an equivalent level in cryopreserved and fresh PBLs. In 5/6 experiments, cytotoxicity generated from cryopreserved PBLs reached maximal levels equivalent to those of fresh PBL at the same or one-fold different numbers of responding cells. Use of either EBV-transformed autologous cells or autologous leukemia cells for in vitro sensitization produced approx the same cytotoxicity response whether cryopreserved or fresh PBLs were used. In 2/5 experiments with in vitro sensitization of the PBLs of a 36-yr-old patient with acute myelogenous leukemia against his own leukemia cells, his PBLs reacted to his leukemia cells without addition of an immune modulator in vitro. This activity was lost when cryopreserved PBLs were used, but when the PBLs were co-incubated with his autologous leukemia cells in the presence of Nocardia rubra cell wall skeleton (N-CWS) for 7 days, the cytotoxicity on autologous leukemia target cells reappeared. Removal of N-CWS just prior to assay did not change the outcome of the assay. (15 Refs)

58. IDENTIFICATION AND ISOLATION OF THE MAIN COMPONENT (GP350-GP220) OF EPSTEIN-BARR VIRUS RESPONSIBLE FOR GENERATING NEUTRALIZING ANTIBODIES IN VIVO.

Thorley-Lawson DA, Poodry CA
Dept. Pathology and Medicine, Div. Geographic Medicine, Tufts Univ. Sch. Medicine, Boston, MA, 02111
J Virol; 43(2):730-736 1982

The majority of hybridomas we have characterized against Epstein-Barr virions react with the major glycoproteins gp350 and gp220 (gp350/220). One of these antibodies, ID4C-1, neutralizes virus infection in vitro. The presence of gp350/220 on the viral envelope could be confirmed directly by immunoelectron microscopy. We used lectin affinity (ricin) and immunoaffinity (ID4C-1) to purify gp350/220 and show that this material is able to induce potent virus-neutralizing antibodies. Absorption of four human and one rabbit anti-Epstein-Barr virus sera with purified gp350/220 suggests that this is the primary component responsible for generating neutralizing antibodies in vivo. (Author abstract) (24 Refs)

59. DETECTION OF IMMUNOGLOBULIN M ANTIBODY TO EPSTEIN-BARR VIRUS BY USE OF AN ENZYME-LABELED ANTIGEN.

Schmitz H
Abteilung fur Virologie, Bernhard-Nocht Institut, D-2000 Hamburg 4, W. Germany
J Clin Microbiol; 16(2):361-366 1982

Microtiter plates coated with anti-mu-chain antiserum and enzyme-labeled Epstein-Barr virus (EBV) antigen were used to detect IgM antibodies to EBV. A comparison of four different methods for detection of acute EBV infections demonstrated that a combination of the enzyme-labeled antigen-IgM test with the detection of antibodies to either Epstein-Barr nuclear antigen or heterophile antigen was highly specific and sensitive. IgA antibodies to EBV could be detected when the solid phase was changed. (18 Refs)

60. P105, AN EBV-INDUCED TARGET OF THE IMMUNE RESPONSE (MEETING ABSTRACT).

Jones W, Casareale D, Reisert PS, Spiro RC, Sairenji T, Humphreys RE
University of Massachusetts Medical School, Worcester, MA, 01605
Fed Proc; 41(3):803 1982

In order to characterize EBV-induced targets of the immune response, a 00 dalton glycoprotein prominently recognized in immunoprecipitates of, Burkitt's lymphoma patients' sera with P3HR-1 EBV-superinfected Raji cells (S-Raji), was analyzed through the use of a specific heteroantiserum. Synthesis of p105 was restricted to EBV-superinfection and was not blocked with phosphonoacetic acid, indicating p105 to be an 'early' viral antigen. An external exposure of p105 on the cell surface was indicated by its glycosylation with radiolabeled sugars, by antibody binding in a radioimmunoassay with living cells and by membrane immunofluorescence. Although anti-p105 serum did not neutralize P3HR-1 virus (but bound to P3HR-1 cell membranes), it mediated antibody-dependent cellular cytotoxicity (ADCC) to EBV-superinfected Raji and to control Raji cells but not to several EBV genome-negative cell lines. We conclude that p105 is an EBV-induced, external, glycosylated, early membrane antigen to which EBV-infected patients generate a substantial antibody response. These antibodies do not neutralize infectious virus but might mediate ADCC to, or otherwise affect, infected cells early in the virus cycle. (no Refs)

61. IMMUNOCHEMICAL CHARACTERIZATION OF EBV ANTIGENS DETECTED BY DOUBLE IMMUNODIFFUSION.

Sternas L, Kallin B, Luka J, Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Intervirology; 17(4):208-214 1982

Double immunodiffusion (Ouchterlony) tests gave regularly positive reactions when extracts of [35S]-methionine-labeled, n-butyrate-induced P3HR-1 cells were allowed to react with serum pools with high Epstein-Barr virus (EBV) antibody titers from Burkitt lymphoma or nasopharyngeal carcinoma patients, but not with EBV antibody-negative sera. Similarly prepared extracts of noninduced P3HR-1 cells gave no precipitation lines with the antibody-positive sera. The composition of the precipitates was analyzed by SDS-PAGE and compared with immunoprecipitates obtained by indirect immunoprecipitation in soln. Three lines precipitated on the Ouchterlony plate were analyzed; these lines were located at close (a), intermediate (b), and distant (c) positions in relation to the antigen well. Precipitate (a) contained polypeptides with mol wt of 165,000 (165K), 152K, 138K, 134K, 103K, and 55K. Precipitate (b) contained 152K and 138K as the major components, while 55K was relatively underrepresented. Precipitate (c) contained 90K and 55K as major components, while 152K was a minor component. The method is suitable for the study of possible subtype differences between defined antigenic components of the early and late EBV-determined antigen complexes. (Author abstract) (9 Refs)

62. BLA: A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN DEFINED BY A MONOCLONAL ANTIBODY (MEETING ABSTRACT).

Wiels J, Lipinski M, Fellous M, Tursz T
No affiliation given
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

A rat monoclonal IgM antibody (38-13) has been raised against Daudi cells, derived from a Burkitt lymphoma (BL). This antibody defined an antigen, referred to as BLA, specifically expressed on Burkitt tumor cells, whether they contain the Epstein-Barr virus (EBV) genome or not. BLA is not detected on EBV-positive lymptoblastoid cell lines, normal or mitogen activated lymphocytes, or fresh malignant cells from patients affected with various non-BL lymphoproliferative disorders. Therefore, 38-13 recognizes a BL-associated antigen clearly not related to EBV. Biochemical analysis indicates that BLA is a hydrophobic glycoconjugate: the antigen resists proteolytic treatments; no specific protein is detected by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) analysis after precipitation of radio-labeled BL membranes with 38-13; the antibody is specifically absorbed by a chloroform-methanol extract of BL cells; immunofluorescence staining for BLA is inhibited in the presence of D-galactose, N-acetylneuraminic acid and N-acetyl-D-galactosamine. Since it displays an apparent specificity for BL cells, the 38-13 monoclonal antibody could represent a valuable tool for diagnosis and specific immunotherapy of BL. (no Refs)

63. ANALYSIS OF THE EPITHELIAL AND LYMPHOID CELLS IN NASOPHARYNGEAL CARCINOMA BIOPSIES USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Iliescu V, Crawford DH, De The GB, Ellouz R
Imperial Cancer Research Fund, London, WC1E 6JJ, England
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Anaplastic nasopharyngeal carcinoma (NPC) is a geographically restricted tumor which occurs most commonly in Southern China and in certain areas of North Africa. The tumor usually arises in the Fossa of Rosenmuller and metastasizes early to the cervical lymph nodes. Complete surgical removal is often impossible and so treatment is usually by radiotherapy. NPC is etiologically associated with Epstein Barr virus (EBV) and the malignant epithelial cells express the EB viral nuclear antigen (EBNA). The tumor tissue is heavily infiltrated with lymphocytes which have been shown to be of both B and T cell types. The B cells secrete IgA antibodies directed against the EB viral capsid and these antibodies can be found in the saliva of most NPC patients. In the present study we have used monoclonal antibodies to T and B cell subsets to further define the infiltrating lymphocyte populations. We have used double staining techniques with rhodamine and fluoresein-labelled antibodies to stain the malignant epithelial cells for EBNA and the various lymphocyte subpopulations on the same sections in order to visualize the inter-relationships between these cells. The results will be discussed in relation to the probable immunological events occurring within these tumors. (no Refs)

64. MONOCLONAL ANTIBODIES AGAINST EPSTEIN-BARR VIRUS AND THE PLAN TO USE IMMUNOTOXINS TO TREAT CANCER (MEETING ABSTRACT).

Braun DG
No affiliation given
Experimentelle Tumorforschung in der Hals-Nasen-Ohrenheilkunde, February 25-27, 1982, Dusseldorf, W Germany Universitat Dusseldorf; 1982

Epstein-Barr (EBV) virus causes infectious mononucleosis; it is further regarded as the possible etiologic agent of Burkitt lymphoma and carcinoma of the nasopharynx (NPC). This unequivocal virus association was the reason for our producing monoclonal murine antibodies against membrane-associated virus polypeptide. A report is made on antibodies obtained thus far which are suitable for serological typing of EBV. Using this model the active ingredient of the immunotoxin will be commented upon especially as an alternative and/or as supplemental form of treatment for NPC. (no Refs) (In GER)

65. PERSISTENT ACTIVE INFECTION OF EPSTEIN-BARR VIRUS (EBV) IN CARRIER FEMALES OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP).

Sakamoto K, Seeley JK, Purtilo DT
Second Dept. Surgery, Kumamoto Univ. Medical Sch., Kumamoto 860, Japan
Excerpta Med Int Congr Ser; 571:375-379 1982

Among conditions that may follow infection with Epstein-Barr virus (EBV), is malignant lymphoma in males affected by the X-linked lymphoproliferative syndrome (XLP). To test the hypothesis that the variable expression of XLP is manifested in obligate carrier females, blood from 12 obligate carrier females was studied for anti-viral capsid antigen (VCA), anti-early antigen (anti-EA) and anti-Epstein-Barr nuclear-associated antigen (EBNA). All carriers were seropositive to EBV. The reciprocal geometric mean titer for IgG anti-VCA was elevated to 570 in the carrier females compared to 100 in 24 controls. The range of anti-VCA was from 80 to 5,120. IgA class anti-VCA was found in 2/3 of the carriers. All but one of those with anti-VCA of IgA class showed anti-EA, indicative of active infection and immunodeficiency. About one-half of the carriers had persistent anti-EA antibodies. However, the anti-EBNA levels of carrier females were similar to those of the healthy controls. There was no apparent relationship between IgM level and EBV-specific antibody titers. The paradoxically elevated EBV-specific antibodies which tend to persist in obligate carriers of XLP provides an opportunity to define the immunopathology of XLP and to detect carrier females. (17 Refs)

66. ANTIUROGENITAL TUMOR MONOCLONAL ANTIBODY BINDS TO CELLS TRANSFORMED BY CYTOMEGALOVIRUS ISOLATED FROM HUMAN PROSTATE (MEETING ABSTRACT).

Wright GL, Starling JJ, Beckett ML, Martin D
Eastern Virginia Medical School, Norfolk, VA
Hybridoma; 1(2):207 1982

Monoclonal antibody DU83-21-4 was produced by fusion of spleen cells from Balb/c mice immunized against the prostate adenocarcinoma cell line DU145 and the P3x63/Ag8 mouse myeloma line. Antibody binding specificity was determined by an in vitro binding radioimmunoassay, a membrane immunofluorescent assay, a biotin/avidin immunohistochemical assay, and a complement-dependent cytotoxicity assay. Competitive-binding, blocking and adsorption variations of these assays were also used as an additional check on the immunologic specificity of the DU83-21-4 antibodies. The hybrid producing this monoclonal antibody has been cloned four times and adapted to grow in chemically defined medium. Immunodiffusion, immunoprecipitation, and trans-blot techniques suggest that the DU83-21-4 antibody is a IgM(k) that binds to antigenic determinants present in both a 210 and 97K protein. The DU83-21-4 antibodies bind to a membrane antigen present on both prostate and bladder tumor cells but not to other urogenital, normal and malignant human cell lines and tissues. Further specificity studies demonstrated that this antibody did not bind to oncodevelopmental markers, prostate differentiation markers, HLA, DR, beta2-microglobulin or fibronectin. The DU83-21-4 antibody was found to crossreact with surface antigens present on a human embryonic lung cell line transformed by a cytomegalovirus (CMV) isolated from a normal neonatal human prostate gland. No binding was observed with (a) normal human cells transformed or infected by CMV's isolated from different sources, including the prototype CMV strain, AD169; (b) human cells transformed or infected with EBV; or (c) CMV polypeptide antigens. (no Refs)

67. MONOCLONAL ANTIBODY DU83-21-4 MEDIATES CYTOTOXICITY TO HUMAN PROSTATE AND BLADDER TUMOR CELLS (MEETING ABSTRACT).

Wright GL, Starling JJ, Beckett ML
Eastern Virginia Medical School, Norfolk, VA, 23501
Fed Proc; 41(3):552 1982

The specificity of the monoclonal antibody DU83-21-4, which was generated by fusing spleen cells from Balb/c mice immunized against the prostate adenocarcinoma cell line DU145 and P3x63/Ag8 mouse myeloma cells, was determined by a radioimmunoassay and a membrane immunofluorescent assay. The DU83-21-4 binds to membrane antigens on both prostate and urinary bladder tumor cells but not to 41 other normal and malignant human cell lines and tissues. Further specificity studies suggest DU83-21-4 antibodies do not bind oncodevelopmental markers (CEA (carcinoembryonic antigen), AFP (alpha-fetoprotein)), prostate differentiation markers (PAP, PA), HLA, DR or fibronectin. These antibodies also crossreact with a surface antigen on a human embryonic lung cell line (CMV-Mj-HEL-1) transformed by a cytomegalovirus (CMV) isolated from a human prostate gland, but not to CMV polypeptide antigens or other human cells transformed or infected by CMV virus. The DU83-21-4 antibodies mediate complement-dependent and antibody-dependent cytotoxicity to prostate and bladder tumor cells and the CMV-Mj-HEL-1 cells but not other normal and malignant cells. The crossreactivity of the DU83-21-4 antibody with the CMV transformed line and its reactivity with prostate and bladder tumors may be significant in view of the high incidence of herpes-like viruses with the human urogenital tract. (no Refs)

68. STUDY OF ANTIBODIES TO ADENOVIRUSES IN PATIENTS WITH TUMORS OF THE UROGENITAL SYSTEM.

Csata S, Kulcsar G, Horvath J, Nasz I, Ongradi J, Verebelyi A
Dept. Urology, Istvan Municipal Hosp., Budapest, Hungary
Int Urol Nephrol; 14(2):115-119 1982

Assays for antibodies to adenoviruses (AV) were conducted on approx 4,000 samples of sera from 516 patients including 193 with non-neoplastic diseases of the urogenital system, 253 with urogenital tumors, and 70 with nonurological organic diseases. Malignant tumors included 57 bladder, 32 prostatic, 15 renal, 15 testicular, and 23 other tumors. Benign tumors included 18 papillomas of the bladder, 4 urethral polyps, and 89 hypertrophies of the prostate. Antibodies were measured by the complement fixation reaction. Viruses and early antigens tested included AV Type 1 and 5 (of latent properties), AV Type 12 and 18 (of oncogenic capacity), and early non-virion antigens of AV Type 1, 5, 12, and 18. HEp cell extract served as a control. Results were similar for AV-1 and AV-5 and for AV-12 and AV-18. Complete AV-1 was found in 19% of the patients with urogenital tumors, 34% of the patients with non-neoplastic urogenital disease, and 12% of the patients with nonurological disease. The respective occurrences of early AV-1 antigens were 56%, 23%, and 33%. The respective occurrences of complete AV-12 antigens were 13%, 6%, and 2%. The respective occurrences of early AV-12 antigens were 53%, 18%, and 4%. Antibodies to non-virion antigens of oncogenic AV were thus more common in patients with urogenital tumors than in other patients, suggesting that defective forms of oncogenic AV are present and operating in many tumor patients. Antibodies of AV of latent character were more common among patients with non-neoplastic diseases. Data suggest that oncogenic AV are involved in tumors of the urogenital system. (24 Refs)

69. A MONOCLONAL ANTIBODY DETECTING THE ADENOVIRUS TYPE 5 E 1B-58KD TUMOR ANTIGEN: CHARACTERIZATION OF THE E 1B-58KD TUMOR ANTIGEN IN ADENOVIRUS-INFECTED AND -TRANSFORMED CELLS.

Sarnow P, Sullivan CA, Levine AJ
(c/o Levine) Dept. Microbiology, Sch. Medicine, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Virology; 120(2):510-517 1982

A monoclonal antibody directed against the adenovirus Type 5 Elb-58Kd tumor antigen has been isolated. Immune clearing experiments were employed to demonstrate that this monoclonal antibody detects the same Elb-58Kd antigen observed previously with polyclonal antisera from hamsters bearing adenovirus-induced tumors. Fluorescent antibody tests using the monoclonal antibodies directed against the Elb-58Kd antigen localized the viral protein predominantly in the nucleus of virus-infected and -transformed cells. The monoclonal and polyclonal tumor sera detected similar protein species in virus-infected and -transformed cells. In adenovirus productively infected human cells the monoclonal antibody and polyclonal tumor sera both detected a 25K protein in addition to the Elb-58Kd antigen. In transformed mouse and hamster cells this monoclonal and polyclonal antisera coimmunoprecipitated a 53Kd cellular protein along with the Elb-58Kd antigen. This 53Kd cellular protein is similar to the p53 antigens detected in a variety of transformed cells. (Author abstract) (25 Refs)

70. AUTOLOGOUS ANTIBODIES TO MENINGIOMA CELL SURFACE ANTIGENS.

Pfreundschuh M, Rohrich M, Piotrowksi W, Penzholz H, Fischer H
Med. Univ. Poliklinik, Hospitalstr. 3, 6900 Heidelberg, W. Germany
Anticancer Res; 1(6):367-372 1981

Serum reactivity against cell surface antigens of autologous meningioma cells was investigated in sera of 32 patients with meningioma. Each serum was tested in three serological rosetting assays, protein-A assay (PA), immune adherence assay (IA), and anti-C3 mixed hemadsorption assay (C3-MHA). PA detected antibody in sera of 6 patients, IA detected reactivity in approx half the patients, whereas C3-MHA detected serum reactivity in 26 patients. In 13 patients, autologous serum reactivity was high enough to permit analysis of the reaction by absorption tests. The cell surface antigen specificity of cultured meningioma cells was quite variable, but no antigen specific for meningiomas or brain tumors could be detected. In some patients both preoperative and postoperative sera were tested. No significant change was observed in serum reactivity. No correlation could be found between clinical findings and the course of anti-meningioma antibody titer. Anti-SV 40 reactivity of sera was tested by immunofluorescence against SV 40 antigens. No correlation was observed between the occurrence of anti-SV 40 reactivity and reactivity to autologous cultured meningioma cells. (18 Refs)

71. HISTOCOMPATIBILITY ANTIGENS IN VIRAL WARTS.

Friedman-Birnbaum R, Haim S, Sheinkman A, Gideone O, Barzilai A
Dept. Dermatology, Rambam Medical Center, Haifa, Israel
Acta Derm Venereol (Stockh); 62(1):72-73 1982

One hundred patients with viral warts and 108 apparently healthy matched controls were typed for HLA-A and B antigens. No significant difference in the frequencies of antigens was revealed, which suggested that a possible genetic trend in warts is at least not related to A and B loci of the histocompatibility system. (Author abstract) (6 Refs)

72. MOLECULAR CHARACTERIZATION OF HUMAN TUMOR ANTIGENS (AG) USING HUMAN SERA (MEETING ABSTRACT).

DuBois DB, Cailleau R, Rossen RD
Veterans Administration Medical Center, Baylor College of Medicine, Houston, TX, 77211
Fed Proc; 41(3):409 1982

Sera from 20 normal, 18 malignant melanoma and 22 breast cancer patients were tested against extracts from seven breast cancer, three malignant melanoma and one teratocarcinoma cell line. Tumor extracts, fractionated by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), were transferred electrophoretically to nitrocellulose paper. Resulting electroblots were incubated in dilute sera, washed and then tested for bound immunoglobulin (Ig) using peroxidase-labeled anti-human Ig. Between 12 and 23 discrete Ag were identified, only three of which were also found on normal human fibroblasts. Sera from a few breast cancer patients recognized all 23 Ag. However most recognized one or more subsets of these when tested against both autologous and allogeneic tumor cells. End point dilution analysis showed that a 52,000 (52K) dalton protein was the most abundant Ag in extracts of these tumor lines. A monoclonal antibody (Ab), (clone 122) reactive with p53, a non-viral transformation antigen, specifically precipitated the 52K Ag, indicating that p53 and the 52K Ag, share at least one epitope. WI-38 VA-13, an SV40 transformed line derived from WI-38 also expresses this Ag, which is not found in normal WI-38. These results suggest that there is a large array of common Ags expressed by human tumor cells, which can be identified by Ab in sera of cancer patients and certain normal donors. (no Refs)

VIRAL STUDIES IN HUMAN CANCER

73. HEALTHY CARRIERS OF A HUMAN RETROVIRUS, ADULT T-CELL LEUKEMIA VIRUS (ATLV): DEMONSTRATION BY CLONAL CULTURE OF ATLV-CARRYING T CELLS FROM PERIPHERAL BLOOD.

Gotoh YI, Sugamura K, Hinuma Y
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 79(15):4780-4782 1982

Adult T-cell leukemia virus (ATLV) or ATLV-associated antigen (ATLA)-positive cell clones were isolated from peripheral blood lymphocytes of all five anti-ATLA-seropositive healthy adults tested by a limiting-dilution culture method in the presence of T-cell growth factor (TCGF) but from none of six seronegative adults similarly tested. Although ATLA-positive cells were not always detected in mass cultures of the seropositive lymphocytes, they were found consistently in T-cell cloned cultures of those lymphocytes. Continuous cultures of the ATLA-positive clones obtained were dependent on TCGF. Five clones derives from each of the five donors were maintained for greater than 4 mo and, during culture, all of them acquired the ability to grow without added TCGF. The ATLA-positive clones formed rosettes with erythrocytes and expressed Leu 1, Leu 3a, and Leu 4 antigens but not Leu 2a antigen. These results indicate that anti-ATLA-seropositive healthy individuals carry ATLV in T cells circulating in their peripheral blood. (Author abstract) (12 Refs)

74. T CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND IMMUNOLOGICAL FEATURES OF THE EUROPEAN VARIANT OF THE DISEASE (MEETING ABSTRACT).

Pandolfi F, DeRossi G, Pezzuto A, Ranucci I, Quinti F, Mandelli F
Dept. of Clinical Immunology, University of Rome, Rome, Italy
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

T chronic lymphocytic leukemia (T-CLL) is a rare disease in Europe. This disease is relatively more frequent in Japan where it is designated as adult T cell leukemia (ATL). We observed 10 cases of T-CLL. Peripheral T-CLL cells were studied with surface markers, functional activities and morphology. Results indicate that European T-CLL and Japanese ATL are two discrete diseases. In contrast to ATL, the majority of our cases had: an indolent clinical course; lack of lympho-, hepato-, spleno-megaly; lack of natural antibodies against a retrovirus type C designed HTLV (human thymus leukemia virus); heterogeneity of surface phenotypes. Skin lesions and nuclear convolutions were observed only in cases with the OXT4+, 3A1-phenotype. The morphology in 5 cases was typical of a large granular lymphocyte. Growth of cultured T cells from these patients was achieved by the use of both PHA (phytohemagglutinin)-containing and PHA-free IL-2, but analysis with monoclonal antibodies showed that the growing cells were the normal contaminating ones. We conclude that European T-CLL is a distinctive disease. (no Refs)

75. BIOLOGICAL CARCINOGENESIS.

Rich MA, Furmanski F
AMC Cancer Res. Center and Hosp., Lakewood, CO
Biological Carcinogenesis. New York, Marcel Dekker, Inc., 310 pp., 1982.

The general principles which govern carcinogenesis are identified for each of the major classes of carcinogens and the extent to which these principles are applicable to the carcinogenic process induced by other classes of agents is determined. Current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive are described. Mechanisms in viral carcinogenesis are discussed with respect to: T-cell growth, T-cell growth factor, T-cell leukemias and lymphomas and isolation of a new type-C retrovirus, properties of sarcoma growth factors produced by sarcoma virus transformed cells, and interactions of murine leukemia viruses with hematopoietic stem cells. Mechanisms in chemical carcinogenesis are discussed with respect to activation of carcinogenic polycyclic hydrocarbons by metabolism, involvement of a protein kinase in multistage skin tumor promotion, and the effect of tumor-causing chemicals on the control of mutagenesis and differentiation in mammalian cells. Transformation of cloned mammary epithelial cells following combined treatment with mouse mammary tumor virus and dimethylbenz(a)anthracene, virus-cell interactions during hormonal carcinogenesis, and separate pathways for viral and chemical carcinogenesis in the mouse mammary gland are described. A molecular approach to studies of chemical carcinogen-virus interaction is presented. Other presentations deal with multistage recombinational origin of leukemogenic viruses, radiation-induced leukemogenesis, neoplastic transformation of cultured cells by herpes simplex virus type 2 and carcinogens, modulation of adenovirus transformation and replication, and transformation of murine fibroblasts. (682 Refs)

76. HERPETIC VIRUSES.

Nahmias AJ
No affiliation given
Gaz Med Fr; 89(22):2571,2573-2574 1982

Herpes viruses (HV) have been associated with Burkitt's lymphoma (Epstein-Barr virus), with cancer of the uterus (herpes simplex virus), and with Kaposi's sarcoma (cytomegalovirus). Vaccinations against HV raise problems associated with latency, carcinogenic potentiality, and more complex immunology. Hyperimmune globulins and transfusions have been used to protect immunologically compromised individuals against HV. (1 Ref) (In FRE)

77. EVIDENCE FOR DEFECTIVE HERPES SIMPLEX VIRUS TYPE 2 IN CERVICAL CANCER CELLS: IMMUNOFLUORESCENT DETECTION OF VIRAL ANTIGENS AND PROPERTIES OF UV-IRRADIATED HSV-2.

Ver Planck JB, Beth J
Boston University Graduate School, Boston, MA
Diss Abstr Int [B]; 42(6):2238-B 1981

Evidence of defective herpes simplex virus type 2 genomes in cervical cancer cells was sought using the indirect immunofluorescent antibody test. Other parameters used to detect the presence of defective viral genomes included: growth properties in methyl cellulose, reactivation using DNA base analogs, assays for virion excretion and sensitivity to superinfection.

The molecular biology of cell transformation was also explored using uv-irradiated HSV-2 in an in vitro transformation model. HSV-2 uv antigen expression, viral and cellular DNA synthesis and repair were measured using this model. (no Refs)

78. GENITAL HERPES AND CANCER.

Pellisse M
Service du Dr Jean Hewitt, Clinique Tarnier, 89, rue d'Assas, Paris, France
Gaz Med Fr; 89(22):2611-2612,2614 1982

Several international studies have pointed to genital herpes as a factor in the development of uterine cancer. Studies have shown that there are 2x more cases of dysplasia and 8x more uterine cancer in women with genital herpetic lesions than in a not infected population. Cervical cellular anomalies have been detected at the end of 6 yr of surveillance following herpetic infection. Serological studies have demonstrated that 36% of the women who later developed a cancer in situ of the uterus had positive serology for herpes simplex virus. Herpetic antigens have been found in cancer cells and in dysplastic cells of the uterus. Animal studies have revealed that preparations of the virus inactivated by uv light can transform cells and then the transformed cells into tumors. Other factors such as patient age at first pregnancy, the number of pregnancies or other genital infections affect the incidence of infection with herpes simplex. Cancer of the vulva has also been associated with herpes simplex virus infections. Antigens of the virus have been found in the tumor cells of patients with cancer of the vulva. (11 Refs) (In FRE)

79. PRIMARY HERPES INFECTIONS.

Mazeron MC, Ferchal F
Service de Bacteriologie-Virologie, Hopital Saint-Louis Universite Paris VII, 2, place du Dr Fournier, 75010 Paris, France
Gaz Med Fr; 89(22):2591-2592,2595-2596,2598-2600 1982

Herpes simplex virus Type (HSV 1) is the cause of herpes infections above the waist and herpes simplex virus Type 2 (HSV 2) usually causes infections below the waist. HSV 1 in the primary infection causes ulcerative gingivostomatitis, herpetic esophagitis, and rarely, conjunctivitis. Kaposi-Juliusberg syndrome is a severe infection which occurs in a patient with atopic eczema. Herpetic encephalitis is the most serious neurological manifestation of HSV 1 with a 50-70% mortality of untreated cases. The primary infection with HSV 2 is a sexually transmitted disease. Urogenital herpetic infections are frequently accompanied by neurological manifestations. The diagnosis of herpes depends on the isolation of the virus from the lesions, and a distinction between the two types of virus can be made on the basis of immunological testing. Tzanck cells are diagnostic for Herpes. A serologic diagnosis depends on a significant rise in antibody titer in serum taken two wk after infection when compared to taken at the start of the infection. Acyclovir is a new antiherpes drug which shows some promise of being nontoxic and having a very selective antiviral action. (27 Refs) (In FRE)

80. HERPES SIMPLEX VIRUS AND CANCER.

Lehtinen M, Lehtinen T, Leinikki P
Biomedical Inst., Univ. Tampere, PL 607, 33101 Tampere 10, Finland
Duodecim; 98(9):664-673 1982

Herpes simplex virus (HSV) has been a suspected cause of cancer for a long time, and especially for cervical cancer. It has never been clear whether HSV is the 'driver' or the 'passenger.' The literature on this subject is discussed in detail under six headings: epidemiological correlation, tumor-specific antigens, malignancy-inducing capacity of HSV in cells, presence of HSV in tissue samples, animal experiments, and prevention. (61 Refs) (In FIN)

81. CLINICAL AND VIROLOGICAL ASPECTS OF FEMALE GENITAL HERPES IN JAPAN.

Kawana T, Chen JT, Yoshikawa H, Yoshida R, Nagano M, Sakamoto S

Dept. Obstetrics and Gynecology, Tokyo Univ. Sch. Medicine, 7-3-1-Hongo, Bunkyo-ku, Tokyo 113, Japan

Excerpta Med Int Congr Ser; 571:339-350 1982

The clinical and virological aspects of herpes simplex virus (HSV) Type I and II isolated from 131 female outpatients is discussed. Included is consideration of relationship between HSV type and clinical classification, serum antibody distribution in relation to clinical type, etiological considerations, treatment of acute and recurrent genital herpes, recurrence rate, and asymptomatic virus secretors. A previous study of a search for HSV in the female genital tract of 385 patients with various conditions, disclosed one positive case of HSV-2 among 128 with invasive cervical cancer and none in six cases of endometrial cancer. In a related search in the male genital tracts of 182 patients, one positive HSV-2 was found in prostate fluid of 25 cases of prostate hypertrophy but no positive cases in 21 with prostate cancer. Examination of tissues disclosed no positive cases among 6 patients with prostate cancer, and 17 with prostate hypertrophy. The prevalence rate in this series of 182 patients, 0.5%, is much lower than that in the United States. (18 Refs)

82. LYMPHOEPITHELIAL CARCINOMA OF THE OROPHARYNX: INCIDENCE AND DIFFERENTIAL DIAGNOSIS.

Sesterhenn K, Krueger GR, Bertram G, Sesterhenn I

Universitats-HNO-Klinik, Joseph-Stelzmann-Strasse 9, D-5000 Koln 41, W. Germany

HNO; 30(7):243-249 1982

From 1960-1980, 452 malignant tumors of the oro- and nasopharynx were observed in the Cologne university ENT-clinic. 313 tumors of the oropharynx and 119 of the nasopharynx could be reclassified using the current classifications of upper respiratory tract tumors (WHO and Cologne modification) and of malignant lymphomas (German Kiel and Rappaport classifications). The analysis showed a different distribution of histological diagnoses in the naso- and oropharynx. Whereas the squamous cell carcinoma dominates with 57% in the oropharynx it is seldom seen (only 13%) in the nasopharynx. The nonkeratinizing and undifferentiated carcinomas showed an inverse distribution in both regions. Malignant lymphomas and other types of malignant tumors occur equally frequent in the naso- and in the oropharynx. Only patients with non-keratinizing and undifferentiated carcinomas of the nasopharynx showed elevated antibody titers against Epstein-Barr virus. Seven patients with tumors of the same histological type but localization in the oropharynx had no elevated antibody titers against EBV. (Author abstract) (43 Refs) (In GER)

83. CARCINOGENESIS FACTORS IN MALIGNANT TUMORS OF THE CERVICAL REGION.

Miyahara Y, Sato T
Dept. Head and Neck Diseases, Osaka Prefectural Center for Adult Diseases, Osaka, Japan
Nippon Jibiinkoka Gakkai Kaiho; 85(3):348-351 1982

Various clinical and epidemiological factors affecting the occurrence of cancers of the head and neck region are discussed. A combination of smoking and masculinity is associated with laryngeal cancer, Epstein-Barr virus is associated with upper pharyngeal cancer, improperly fitting dentures is associated with tongue cancer, heavy alcohol consumption and masculinity is associated with pear-shaped depressed-type lower pharyngeal cancer, and Plummer-Vinson syndrome and being female with lower pharyngeal cartilage cancer. Squamous metaplasia of the supraglottis increases with age, and tobacco smoking promotes such metaplasia. The combined effects of drinking and smoking, as judged by the Brinkmann and Sake indices, are strongly implicated in high rates of supraglottic cancer. Tobacco, aging, aggressive personality, vocal abuse, and masculine traits promote development of glottic cancer. Induction of cancer by radiation has also been observed; in cases of benign diseases, the effects are not observed for an av of 33 yr and in cases of malignant diseases for an av of 10 yr after exposure. (no Refs) (In JPN)

84. GENETIC AND FAMILY STUDIES (MEETING ABSTRACT).

Miller RW
Clinical Epidemiology Branch, National Cancer Institute, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A4 1982

It is important not only to know what causes cancer, but also who is most or least susceptible and why. Family clusters of cancer may occur for genetic reasons. The tumors may be of the same type, of dissimilar types or they may be associated with non-genetic diseases. In one family, for example, seven members developed renal cell carcinoma. The study of unaffected members in the line of descent revealed three more cases. Examination of the chromosomes in lymphocytes and skin fibroblasts revealed that the affected members had a translocation from chromosome 3 to chromosome 8. The patients had no signs of other disease, such as congenital malformations. Examination of relatives too young to have developed renal cell carcinoma revealed that several had the 3/8 translocation and were therefore at high risk of renal cell carcinoma. By frequent examination, the tumor can be detected early, and life-saving treatment promptly administered. Purtilo and his associates have described an X-linked susceptibility to diseases of the B lymphocytes, including lymphoproliferative disorders and fatal infectious mononucleosis. In these families multiple male members develop these diseases, which represent an interaction between host susceptibility and a Epstein-Barr virus (EBV). Production of a vaccine against EBV infection could be tested for its effectiveness in such families. Interactions are also known between host susceptibility and physical agents. The inability of patients with xeroderma pigmentosum to heal DNA damage caused by exposure to sunlight is a case in point. In ataxia-telangiectasia, the patients are unable to heal DNA damage due to gamma radiation exposure. The DNA damage is not the same in the two disorders. Protecting patients with XP from sunlight can prevent or at least delay the occurrence of frequently fatal skin cancer. Protecting patients with AT from therapeutic radiation (for the lymphomas to which they are prone), can prevent acute radiation reaction. From such rarities we have learned a great deal about cancer biology. This new information about host susceptibility and carcinogenic mechanisms may lead to new means for prevention or early detection of cancer. (no Refs)

85. ACQUIRED IMMUNODEFICIENCY AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Geerling J
Afdeling Inwendige Ziekten, Slotervaartziekenhuis, Amsterdam, The Netherlands
Ned Tijdschr Geneeskd; 126(14):631-633 1982

Recent studies on the sudden increase in the incidence of Kaposi's sarcoma mostly in homosexual men abusing drugs are reviewed. The new syndrome is characterized by very poor prognosis and high incidence of infectious disease indicative of impaired cell-mediated immunity. Kaposi's sarcoma is believed to be of viral etiology. Human leukocyte antigen Dr 5 was found in 10/12 patients examined, while the frequency of this antigen is only 12% in the general population. (7 Refs) (In DUT)

86. CYTOMEGALOVIRUS RNA IN KAPOSI'S SARCOMA (MEETING ABSTRACT).

Fenoglio CM, Oster MW, McDougall J
Columbia University, New York, NY
Lab Invest; 46(1):25A 1982

There has been a recent increase in Kaposi's sarcoma (KS) in homosexual males. When KS occurs, in this clinical setting, it resembles the African form of the disease in that it presents with prominent visceral involvement and has a more rapidly progressive clinical course than is usually seen in Americans. Because of the increased incidence of this tumor in immunosuppressed individuals, as well as its African distribution (which resembles somewhat Burkitt's lymphoma), a viral etiology has been postulated. We have recently had the opportunity of studying a 34-year-old homosexual male who had undergone 2 years of chemotherapy for an embryonal carcinoma of the testis and who subsequently developed visceral and cutaneous KS. He had a positive CMV titer of 1 to 8. CMV genetic material was demonstrated in frozen sections of bioptic material from the cutaneous lesions using the in situ hybridization technique for localizing genetic material. (no Refs)

87. CYTOMEGALOVIRUS AND KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN.

Drew WL, Miner RC, Ziegler JL, Gullett JH, Abrams DI, Conant MA, Huang ES, Groundwater JR, Volberding P, Mintz L
Dept. Pathology and Lab. Medicine, Mount Zion Hosp. and Medical Center, P.O. Box 7921, San Francisco, CA, 94120
Lancet; 2(8290):125-127 1982

Ten homosexual men with Kaposi's sarcoma (KS) were studied for evidence of cytomegalovirus (CMV) infection. IgG and IgM antibodies to CMV were detected in nine out of nine and in seven out of nine of these patients, respectively. CMV was recovered from body secretions or peripheral blood of seven patients. Viral cultures of KS tumor biopsy specimens were negative in eight out of eight patients, but CMV RNA was detected by in-situ hybridization in two out of three and CMV antigen(s) by immunofluorescence in six out of nine. Normal tissue specimens from three KS patients were negative for CMV antigen. These observations suggest an association of CMV with KS. (Author abstract) (25 Refs)

88. RISK OF CANCER AFTER HERPES ZOSTER: A POPULATION-BASED STUDY.

Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO
(c/o Kurland) Dept. Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN, 55901
N Engl J Med; 307(7):393-397 1982

The risk of malignant disease in 590 patients with a first episode of herpes zoster (HZ) in the period 1945-1959 was evaluated in a large population-based study. Cases studied included those diagnosed in clinical consultation, emergency-room visits, house calls, nursing-home care, or inpatient treatment. Patients were followed up until death or the last reported visit to any community health facility. Total follow-up was 9389 patient-yr. Cervical cancer and skin cancers other than melanoma were excluded because of the lack of reliable incidence rates for the general population. Thirty-six patients had cancers diagnosed prior to diagnosis of HZ. Cancers were diagnosed subsequent to diagnosis of HZ in 90 patients, compared with an expected 84 patients. Overall cancer risk for HZ patients was 1.1 (95% confidence interval 0.9-1.3), which was not significantly greater than the risk for the general population. Relative risk was not greater during yr 1 after diagnosis of HZ than for yr 2-5 or thereafter. When the incidence of cancers at specific sites was analyzed, the relative risk was greater only for colon cancer (relative risk 2.2) and for bladder cancer in women (relative risk 4.1). No significant increase in risk was found for patients with necrotic lesions, recurrent HZ, disseminated HZ. Relative risk of cancer did not vary with the age of the patient at the time of diagnosis of HZ. Findings indicate that neither investigation of HZ patients for occult cancer nor increased surveillance for cancer after diagnosis of HZ is justified. (31 Refs)

89. ISOLATION OF A HUMAN PAPILLOMAVIRUS FROM A PATIENT WITH EPIDERMODYSPLASIA VERRUCIFORMIS: PRESENCE OF RELATED VIRAL DNA GENOMES IN HUMAN UROGENITAL TUMORS.

Green M, Brackmann KH, Sanders PR, Loewenstein PM, Freel JH, Eisinger M, Switlyk SA
Inst. Molecular Virology, St. Louis Univ. Medical Center, St. Louis, MO, 63110
Proc Natl Acad Sci USA; 79(14,part1):4437-4441 1982

The DNA genome of a human papillomavirus (HPV), tentatively designated HPV-EV, was molecularly cloned from hand and leg lesions of a patient with epidermodysplasia verruciformis, a chronic skin disease associated with a 30% risk of developing cancer. Using stringent hybridization conditions, we observed less than 5% homology between HPV-EV and the cloned genomes of HPV-1, HPV-4, HPV-5, and HPV-5a. HPV-EV DNA showed approx 6% homology with HPV-2 and 36% homology with HPV-3. These data suggest that HPV-EV is partially related to HPV-3. Using 32P-labeled cloned HPV-EV as probe in Southern blot hybridization experiments, we detected HPV-EV-related DNA in the carcinoma in situ (Bowenoid lesion) of the vulva of the patient from which HPV-EV was isolated. HPV-EV-related DNA was detected in 2 of 10 vulva carcinomas and in 2 of 31 cervical carcinomas. Related DNA sequences were found in papillomas from each of two patients with condyloma acuminata (anogenital warts), which is of interest considering that condylomas have been reported to convert occasionally to carcinomas. The positive vulva DNAs were also probed with other cloned HPV DNAs: HPV-1-, HPV-4-, and HPV-5a-related sequences were not detected: HPV-3 and HPV-2 DNA probes detected strong and weak DNA bands, respectively, of the same size as found with HPV-EV. The HPV DNA sequences were present in the positive tumors mainly as free viral DNA moleculars: no evidence for integration into cellular DNA was found. The emerging biological picture with papillomaviruses is that cells transformed by these viruses are maintained in a transformed state by free episomal genomes. Thus, our findings are consistent with the idea, but by no means establish, that HPVs play a role in human cancer by a similar mechanism. (Author abstract) (24 Refs)

90. CERVICAL INTRAEPITHELIAL NEOPLASIA AND 'WARTY' ATYPIA: A STUDY OF COLPOSCOPIC, HISTOLOGICAL AND CYTOLOGICAL CHARACTERISTICS.

Kirkup W, Evans AS, Brough AK, Davis JA, O'Loughlin T, Wilkinson G, Monaghan JM
Dept. Gynaecological Oncology, Queen Elizabeth Hosp., Sheriff Hill, Gateshead, Tyne and Wear NE9 6SX, England
Br J Obstet Gynaecol; 89(7):571-577 1982

A consecutive series of 168 patients referred to the colposcopy clinic because of abnormal cervical cytology were examined for three groups of features. Colposcopic features included indefinite and finger-like lesion outline, satellite lesions, open or non-open mosaic, loop capillaries, and overall impression of non-condylomatous wart virus infection (NCWVI). Histological features included koilocytosis (KO), double nucleation (DN), dyskeratosis, hyperkeratosis, dyskaryosis, frequent mitoses, acanthosis, prominent rete pegs, epithelial pearls and overall impression of NCWVI. Cytological features included KO, DN and dyskeratosis. A group of patients exhibited a cluster of histological features related to possible human papilloma virus infection of the cervical epithelium, particularly KO, DN and dyskeratosis. Two colposcopic findings were significantly increased in these patients, 'finger-like' lesion outline and impression of warty change. Cytological changes previously related to warty lesions were not of common occurrence. Cervical intraepithelial neoplasia was rare in women in whom less than 10 yr had elapsed since first intercourse, whereas lesions showing changes suggestive of a warty etiology were evenly distributed between patients at more and less than 10 yr from first intercourse. (14 Refs)

91. GENITAL WARTS: RECENT ADVANCES.

Oriel JD
Dept. Genito-Urinary Medicine, Univ. Coll Hosp., London, England
Clin Exp Dermatol; 7(4):361-367 1982

The current clinical status of genital warts is reviewed. Skin warts in general are caused by human papillomaviruses. Evidence indicates that genital warts may be caused by a different strain or strains of these viruses from those that cause other warts. Epidemiological evidence strongly suggests that genital warts are sexually transmitted; an association between maternal genital warts and laryngeal papillomas in infants and young children has been demonstrated. Clinical forms and therapy are discussed. (30 Refs)

92. THE CONTRIBUTION OF THE VIRAL THEORY OF TUMOR ORIGIN TO ONCOLOGY.

Mazurenko NP
Center Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(5):7-12 1982

The viral theory of tumor origin has proved to be an important factor of accumulation of fresh evidence and working out new methods and approaches. The paper contains a summary of this evidence and discusses the problem of the indirect co-carcinogenic effect of tumor-inducing agents. Sometimes it is due to their activation of specific oncogenic viruses. In other cases, as the author suggests, it may be caused by the activation of potential oncogenes (protooncogenes) of normal cells. There are viral and non-viral tumors and human tumors are apparently chiefly non-viral. The author suggests that it is an endogenous disease (protooncogenes and their endogenous activators). The author considers his hypothesis on the cellular origin of oncogenes and the similarity of their transmission by viruses to microorganism transduction. A similar suggestion was made by P Vogt and A D Altstein 10 years later and it has been supported by some findings ever since. The viral theory cannot be regarded as the sole fundamental theory of carcinogenesis. (Author abstract) (no Refs) (In RUS)

93. GENITAL KERATINOCYTIC DYSPLASIA.

Kwittken J
P. O. Box K, Tenafly, NJ, 07670
Mt Sinai J Med (NY); 49(4):289-296 1982

Based upon personal experience with 10 cases, this report reflects a distinct clinical and pathologic entity involving the genital skin and mucosa of young adults, all showing histologic features indistinguishable from squamous cell carcinoma in situ. This entity has been known for approx 15 yr and has masqueraded under a variety of terms which include bowenoid atypia of the vulva, vulvar atypia, multicentric pigmented Bowen's disease of the genitalia, multiple bowenoid papules of the penis, squamous cell carcinoma of the penis in young men and bowenoid papulosis. This entity encompasses a spectrum of different disorders which include bona fide in situ carcinoma (Bowen's disease), benign possibly viral-induced atypia and in situ carcinoma or benign atypia induced by viruses and/or podophyllin (long term effect) or other local irritative agents or factors on pre-existing lesions such as warts, seborrheic kerotoses or skin tags. Because all of the foregoing nomenclature is inappropriate, I recommend that this entity be termed genital keratinocytic dysplasia, biologic potential undetermined, and that the patient be treated conservatively. (Author abstract) (13 Refs)

94. SQUAMOUS CELL CARCINOMAS.

Grosshans E
Clinique dermatologique, 1, place de l'Hopital, 67091 Strasbourg, France
Rev Prat; 32(31):2111-2116,2119 1982

Dermatological squamous cell carcinomas (DSCC) usually develop on pre-existing lesions in older (over 60 yr old) patients who are in jobs or areas where they receive excessive uv radiation from the sun. Other causes or predisposing conditions of DSCC are medical x-rays, hydrocarbons, arsenic, xeroderma pigmentosum, and cutaneous tumors caused by potentially malignant oncogenic viruses. Ulcerous forms are most frequently found on extremities and mucocutaneous junction. Verrucous forms are most commonly found at the labial commissures, the buccal mucosa, and the genital organs. The lower lip is the size of 50% of the most common pre- disposing condition for DSCC. Increased risk of metastasis is associated with ulcerated carcinomas, invasive and undifferentiated carcinoma, carcinomas of the extremities, ear, lower lip, external genitalia, and carcinomas complicating leg ulcers, scars, and radiodermatitis. A differential diagnosis of DSCC must include then rule out a keratoacanthoma which is a benign tumor that is ofter localized, like DSCC, on the face, on the site of actinic keratoses. (7 Refs) (In FRE)

95. THE RELATIONSHIP BETWEEN HEPATITIS B ANTIGEN AND PRIMARY LIVER CANCER.

Zhang F
Anti-epidemic Station, Manning District, Guarjxi Province, Nanning, People's Republic of China
Zhonghua Liuxingbingxue Zazhi; 3(1):49-52 1982

Two villages, S and Y, only 1,800 feet apart were investigated to determine why they showed a drastically different incidence of primary hepatoma. S had an incidence of 328.73 per 100,000 persons, whereas Y had none in 15 years. The incidence had a remarkable familial aggregation phenomena. Among 20 persons who died, 15 were from 7 families with the remaining 5 also being related to the 7 families. Natural conditions of the villages, living conditions, customs, cultures, and foods consumed were very similar in both villages. No significant differences were found in the content of aflatoxin B1 in the food of both villages. A significantly different distribution of hepatitis B-related events was found. The number of hepatitis B antigen carriers in S was clearly higher than that in Y (p less than 0.05), and more people in S than in Y had a high level of anti-hepatitis B antibody (p less than 0.001). explaining why hepatitis B viral infection rate was greatly higher in S than in Y. The rate of enlarged liver and the rate of viral hepatitis (70% were hepatitis B) were higher in S than in Y. However, no significant differences were seen between the two villages in the rate of liver function abnormality, which was found to be 42.8% for S and 51.12% for Y. Further investigation is needed to clarify these findings, which support the assumption that the hepatitis B antigen is closely related to the incidence of hepatoma. (7 Refs) (In CHI)

96. PRIMARY HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS.

Blumberg BS, London WT
Dept. Medicine, Univ. Pennsylvania, Philadelphia, PA
Curr Probl Cancer; 6(12):1-23 1982

The history, pathobiology, prevention and etiology of hepatocellular carcinoma (HPC) associated with hepatitis B virus (HBV)-infection are reviewed. There is now substantial evidence to support the hypothesis that persistent HBV infection is required for the development of PHC. Prevention of infection with HBV will result in prevention of most cases of HBV. Strategies of primary prevention, intrafamily transmission, insect transmission, and a cellular model for primary hepatocellular carcinoma are among other topics discussed. The proposed model suggests an approach to cancer therapy different from that usually used. While most conventional therapies are directed toward the total destruction of cancer cells, with the side-effect of normal tissue damage, the model suggests that the viability of infected noncancerous cells should be enhanced so that their numbers relative to those cells with integrated HBV DNA will increase and thereby prevent the continued growth of tumors. (35 Refs)

INHIBITORS OF VIRAL FUNCTION AND REPLICATION

97. PRECLINICAL TOXICOLOGY PROFILE OF ACYCLOVIR: AN OVERVIEW.

Tucker WE
Dept. Toxicology and Experimental Pathology, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):27-30 1982

Numerous and extensive toxicologic studies of acyclovir using animal and in vitro assays indicated a low order of toxicity for this antiviral nucleoside analog. Primary cytotoxic effects occurred only at extremely high drug concentrations in plasma or tissue cultures. This correlates well with the high selectivity of the drug for herpes viruses and its low toxicity for uninfected cells in tissue culture. Secondary toxicity in the form of precipitation of acyclovir crystals in the lower nephron of the kidney occurred after rapid intravenous bolus injection causing transient impairment of renal function in the dog and obstructive nephropathy in the rat. These secondary effects were related to the relatively low solubility of acyclovir in the urine. Dermal and ophthalmic formulations were well-tolerated. No significant primary irritation nor systemic toxic manifestations were associated with the application of these materials. A test in guinea pigs gave no indication that acyclovir has sensitization potential. Acyclovir had no effect on reproductive processes or prenatal, perinatal, or postnatal development of offspring in studies with rats, rabbits, and mice. Positive results occurred in 2 of 11 in vitro mutagenicity assays. These involved chromosomal damage at extremely high drug concentrations. In contrast, no evidence of chromosomal damage occurred in three in vivo assays at nontoxic dosage levels and under conditions more relevant to clinical use of the drug. While one of two cell transformation assays gave positive results, no oncogenic potential for acyclovir was indicated by lifetime carcinogenicity bioassays in rats and mice. Numerous in vitro and in vivo assays gave no indication that acyclovir might significantly alter immunologic responses at clinically relevant doses. (Author abstract) (7 Refs)

98. ACYCLOVIR TOLERANCE IN HUMANS.

Keeney RE, Kirk LE, Bridgen D
Dept. Clinical Investigation, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC, 27709
Am J Med; 73(1A):176-181 1982

Acyclovir tolerance has been explored in a broad range of human populations and dosage regimens with intravenous, topical, and oral formulations. Phase I pharmacokinetic/tolerance studies assured safety in special populations at unique risk of complicated herpes infections who were simultaneously at increased risk of toxicity to anti-DNA chemotherapeutic agents. Further safety evaluations accompanied placebo-controlled Phase II studies in infected patients who represent future users of acyclovir. These studies confirm acyclovir as the safest antiherpes agent to be explored in clinical studies to date. (Author abstract) (9 Refs)

99. PERSPECTIVES ON INTERACTIONS OF ACYCLOVIR WITH EPSTEIN-BARR AND OTHER HERPES VIRUSES.

Pagano JS, Datta AK
Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Am J Med; 73(1A):18-26 1982

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] inhibits Epstein-Barr virus (EBV) replication in lymphoblastoid cells at concentrations nontoxic to cellular growth. The mode of action of the drug against EBV differs from the mechanism described in herpes simplex virus systems. Due to the absence of virus-specified thymidine kinase, the drug is poorly phosphorylated in EBV-infected cells. The extent of monophosphorylation is similar both in mock-infected and EBV-infected cells. Despite weak phosphorylation of the drug, the replication of linear EBV DNA is inhibited due to exquisite sensitivity of the viral DNA polymerase. Activation of acyclovir does not require phosphorylation by virus-specified thymidine kinase. Inhibition of different herpes-group viruses depends on three variable factors: degree of phosphorylation, cellular metabolism of the drug, and degree of sensitivity of the viral polymerase. Interaction of acyclovir-triphosphate with EBV DNA polymerase is reversible. Cells infected with EBV and treated with acyclovir resume virus replication following removal of the drug even after long exposure. Acyclovir inhibits replication of linear genomes and stops production of virus, but has no effect on latent cellular infection. These results lead us to predict that acyclovir will suppress, but not cure, EBV infection. (Author abstract) (33 Refs)

100. EFFECT OF ACYCLOVIR ON HERPES SIMPLEX VIRUS REPLICATION IN A PERSISTENTLY INFECTED HUMAN LYMPHOBLASTOID CELL LINE (P3HR-1).

Shaw JE, Colby BM, Leong J, Bolling TJ
Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):72-76 1982

We examined the effect of acyclovir on herpes simplex virus (HSV) replication in the persistently infected human lymphoblastoid cell line, P3HR-1. During 10 days of continuous exposure of P3HR-1 cells to 100 uM acyclovir there was a decrease in the number of cells expressing HSV antigens, the number of copies of HSV DNA per cell, and the infectivity of extracellular virus. A significant increase in each of these was detected after 14 days of continuous exposure of P3HR-1 cells to the drug, demonstrating that the replication of HSV has become resistant to inhibition by acyclovir. No apparent resistance of EBV replication to inhibition by acyclovir, however, was detected in HSV-infected P3HR-1 cells. The number of copies per cell of EBV and HSV DNA increased after exposure of HSV-infected P3HR-1 cells to the tumor promoter TPA (12-O-tetradecanoyl-phorbol-13-acetate). When cells were exposed continuously to acyclovir for 4 mo and then exposed to acyclovir and TPA simultaneously, the number of copies per cell of HSV DNA increased, but the number of copies per cell of EBV DNA increased by only a few, if any. The detection of P3HR-1 cultures of individual cells expressing both HSV and EBV antigens suggested that HSV and EBV productive cycles could occur simultaneously within the same cell. However, single cells very rarely expressed both antigens simultaneously. (Author abstract) (19 Refs)

101. REPLICATION OF EPSTEIN-BARR VIRUS DNA IN LYMPHOBLASTOID CELLS TREATED FOR EXTENDED PERIODS WITH ACYCLOVIR.

Colby BM, Shaw JE, Datta AK, Pagano JS
Cancer Res. Center, Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):77-81 1982

An Epstein-Barr virus (EBV)-producing human lymphoblastoid cell line (P3HR-1) was characterized after prolonged exposure to 9-(2-hydroxyethoxymethyl)guanine (acyclovir).

P3HR-1 cells grown for 11 mo in the presence of acyclovir had the same number of EBV genomes (approx 15/cell) as did short-term acyclovir-treated cells. After removal of the drug, the number of EBV genome equivalents of long-term acyclovir-treated cultures (15/cell) returned to P3HR-1 control levels (340/cell). Indirect immunofluorescence studies demonstrated reduced percentages of long-term (6 to 12 mo) acyclovir-treated P3HR-1 cells expressing both EBV early antigens (EA) and viral capsid antigens (VCA). This contrasts with short-term acyclovir-treated cultures where EA is expressed at normal levels even though VCA expression is reduced. Restriction fragment patterns of the total EBV DNA from both short- and long-term acyclovir-treated cultures were identical with the exception of two fragments present in short- but not long-term acyclovir-treated cultures. EBV-associated DNA polymerase was present in long-term acyclovir-treated cultures with the level of activity, as determined by assay in vitro, comparable to that in untreated P3HR-1 cells. The polymerase activity in the treated cells was sensitive in vitro to acyclovir triphosphate, N-ethylmaleimide (NEM), and phosphonoacetic acid (PAA). These studies demonstrate that acyclovir inhibits the EBV-productive cycle in P3HR-1 cells continuously during extended periods of treatment. (Author abstract) (21 Refs)

102. EFFECT OF ACYCLOVIR ON THE DEOXYRIBONUCLEOSIDE TRIPHOSPHATE POOL LEVELS IN VERO CELLS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 1.

Furman PA, Lambe CU, Nelson DJ
Dept. Experimental Therapy, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):14-17 1982

The effect of acyclovir on the deoxyribonucleoside triphosphate pools of Vero cells infected with herpes simplex virus Type 1 was examined. Deoxyguanosine triphosphate and deoxyadenosine triphosphate pool levels in infected cells treated with acyclovir increased dramatically compared with pool levels in untreated infected cells. The increases were due, a least in part, to inhibition of viral DNA polymerase activity which resulted in reduced utilization of the deoxyribonucleoside triphosphates. Differences of as much as 26x were detected in the sensitivity of herpes simplex virus Type 1 to inhibition by acyclovir with different Vero cell cultures. These results were due to differences in acyclovir triphosphate levels, not to differences in deoxyguanosine triphosphate levels. (Author abstract) (18 Refs)

103. ACYCLOVIR INHIBITION OF VIRAL DNA CHAIN ELONGATION IN HERPES SIMPLEX VIRUS-INFECTED CELLS.

McGuirt PV, Furman PA
Dept. Experimental Therapy, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):67-71 1982

The effect of acyclovir on DNA synthesized in HSV-1-infected cells was examined. Viral DNA synthesis was significantly reduced in the presence of 10 uM acyclovir monitored by cRNA-DNA hybridization and isopycnic centrifugation in cesium chloride. DNA synthesized in infected cells in the presence of acyclovir appeared to be chain-terminated when evaluated by rate zonal centrifugation in alkaline sucrose. Cellular DNA synthesis in actively replicating uninfected cells in the presence of acyclovir was evaluated by isopycnic centrifugation. Cellular DNA synthesis appeared unaffected at concentrations of acyclovir up to 100 uM. (Author abstract) (7 Refs)

104. MECHANISM OF ACTION AND SELECTIVITY OF ACYCLOVIR.

Elion GB
Wellcome Res. Lab., 3030 Cornwallis Road, Research Triangle Park, NC, 27709
Am J Med; 73(1A):7-13 1982

Acyclovir, an acyclic purine nucleoside analog, is a highly potent inhibitor of herpes simplex virus (HSV), Types 1 and 2, and varicella zoster virus, and has extremely low toxicity for the normal host cells. This selectivity is due to the ability of these viruses to code for a viral thymidine kinase capable of phosphorylating acyclovir to a monophosphate; this capability is essentially absent in uninfected cells. The acyclovir monophosphate (acyclo-GMP) is subsequently converted to acyclovir triphosphate (acyclo-GTP) by cellular enzymes. Acyclo-GTP persists in HSV-infected cells for many hr after acyclovir is removed from the medium. The amounts of acyclo-GTP formed in HSV-infected cells are 40 to 100x greater than in uninfected Vero cells. Acyclo-GTP acts as a more potent inhibitor of the viral DNA polymerases than of the cellular polymerases. The DNA polymerases of HSV-1 and HSV-2 also use acyclo-GTP as a substrate and incorporate acyclo-GMP into the DNA primer-template to a much greater extent than do the cellular enzymes. The viral DNA polymerase binds strongly to the acyclo-GMP-terminated template, and is thereby inactivated. (Author abstract) (14 Refs)

105. SPECTRUM OF SENSITIVITY TO ACYCLOVIR OF HERPES SIMPLEX VIRUS CLINICAL ISOLATES.

McLaren C, Sibrack CD, Barry DW
Infectious Diseases Lab., Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC, 27709
Am J Med; 73(1A):376-379 1982

HSV-1 and HSV-2 clinical isolates were tested for their in vitro sensitivity to acyclovir. The median ID50 for 32 genital HSV-2 isolates was 0.215 ug/ml and this was not significantly higher than a median value of 0.125 ug/ml for 28 oral HSV-1 isolates ($p = 0.08$). A wider range of ID50S was observed with the HSV-2 isolates compared with the HSV-1 isolates. The concentration of drug required to inhibit virus replication by 90 and 99% was approximately 10-and 100-fold greater than that producing 50% inhibition. (Author abstract) (12 Refs)

106. DISEASE AND LATENCY CHARACTERISTICS OF CLINICAL HERPES SIMPLEX VIRUS ISOLATES AFTER ACYCLOVIR THERAPY.

Sibrack CD, McLaren C, Barry DW
(c/o Barry), Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):372-375 1982

Herpes simplex virus (HSV) Type 1 from a bone marrow transplant recipient and HSV Type 2 from a patient with genital herpes infection were examined for sensitivity to acyclovir after both patients received therapy with the drug. A 38-and 83-fold shift in sensitivity was detected in association with a marked decrease in viral thymidine kinase activity in isolates from both patients. The resistant HSV-1 isolate was approximately 900x less neurovirulent for BALB/c mice but had similar cutaneous virulence in hairless mice compared with the patient's sensitive strain. In contrast, there was no difference in pathogenicity between the sensitive and resistant HSV-2 isolates. Latency was detected in the trigeminal ganglia of mice after snout inoculation with both the sensitive and resistant HSV-1 isolates. The ganglion isolate from the resistant HSV-inoculated mouse was found to be sensitive to acyclovir, implying a selection for or reversion to the sensitive phenotype. No trigeminal ganglion latency was detected after inoculation with either HSV-2 isolate. Resistance to acyclovir can arise during therapy as a results of diminished viral thymidine kinase activity but does not appear to be associated with increased virulence. (Author abstract) (20 Refs)

107. EFFECT OF 9-(2-HYDROXYETHOXYMETHYL)GUANINE ON VIRAL-SPECIFIC POLYPEPTIDE SYNTHESIS IN HUMAN CYTOMEGALOVIRUS-INFECTED CELLS.

Mar EC, Patel PC, Huang ES
Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Am J Med; 73(1A):82-85 1982

Plaque-forming assay resulted in a 50% inhibitory dose by 9-(2-hydroxyethoxymethyl)guanine (acyclovir) against Towne strain human cytomegalovirus (HCMV) of approximately 98 umol. At the drug concentration of 200 umol, we did not detect any significant inhibition of viral DNA synthesis by cRNA-DNA hybridization. However, at this drug concentration, the synthesis of at least two viral-specific late polypeptides (150K and 67K) was significantly retarded up to 48 hr after infection, but resumed at 72 hr. These data suggest that acyclovir or its in vivo transformed derivative had a transient effect on viral-specific polypeptide synthesis in HCMV-infected human fibroblasts at a high drug concentration. (Author abstract) (19 Refs)

108. RENAL FUNCTION AFTER ACYCLOVIR INTRAVENOUS INJECTION.

Brigden D, Rosling AE, Woods NC
Wellcome Res. Lab., Langley Court, Beckenham, Kent, England
Am J Med; 73(1A):182-185 1982

Plasma urea or creatinine was noted to be raised in 58 of 354 patients treated with intravenous acyclovir. This occurred after intravenous bolus injection of high dosages of acyclovir but the risk was considerably reduced by slow intravenous infusion of the same dosage over 1 hr, with adequate hydration of the patient and adjustment of dosage in patients with preexisting impaired renal function. Animal studies indicate that the impairment of renal function associated with high bolus injections of acyclovir is due to crystal formation in the renal tubules and/or the collecting ducts, and that the crystals are removed after cessation of treatment. The special problems involved in the treatment of patients with herpes encephalitis necessitating limited fluid intake and the possible interaction with other nephrotoxic drugs are discussed. (Author abstract) (3 Refs)

109. ORAL ACYCLOVIR IN THE TREATMENT OF GENITAL HERPES. PRELIMINARY REPORT OF A MULTICENTER TRIAL.

Fiddian AP, Halsos AM, Kinge BR, Nilsen AE, Wikstrom K
Wellcome Res. Lab., Beckenham, Kent BR3 3BS, England
Am J Med; 73(1A):335-337 1982

Ninety patients with genital herpes (29 initial and 61 recurrent episodes) were entered into a double-blind randomized trial of oral acyclovir and placebo. Treatment consisted of 200 mg acyclovir 5x a day for 5 days or matching placebo. Therapy was initiated a mean of 2.8 days and 1.0 days after onset of lesions in initial and recurrent infections respectively. The 13 culture-positive patients with initial disease who received acyclovir had a shorter median duration in days of viral shedding (1.0), pain (3.5), combined symptoms (3.5), time to crusting (3.5), and time to complete healing (5.5) than the 11 culture-positive placebo recipients whose scores were 8.0, 4.5, 4.5, 9.0, and 11.0 respectively (p less than 0.05 for all comparisons). Patients with recurrent disease receiving acyclovir also experienced a reduction in the median duration in days of viral shedding (0.5), time to crusting (men only) (3.0), and time to complete healing (5.0), compared with 2.5, 4.0, and 7.0 days, respectively, for control patients (p less than 0.01 for each variable). New lesion formation was effectively prevented by acyclovir in patients with both initial and recurrent infections (p less than 0.05). Oral acyclovir therapy was well-tolerated and shortened the course of both initial and recurrent genital herpes. (Author abstract) (3 Refs)

110. INTRAVENOUS ACYCLOVIR IN GENITAL HERPES. AN INTERIM REPORT.

Mindel A, Adler MW, Sutherland S, Fiddian AP
Acad. Dept. Genitourinary Medicine, Middlesex Hosp. Medical Sch., London W1, England
Am J Med; 73(1A):347-350 1982

Twenty-five patients with primary genital herpes were treated in a double-blind placebo-controlled randomized trial of intravenous acyclovir. Thirteen patients received the drug and 12 a placebo. Three in each group were male. In the acyclovir group 10 patients had true primary herpes compared with six in the control group. The median time to healing of all lesions was significantly decreased from 11 to 7 days (p less than 0.05), and the median duration of viral shedding from all lesions was decreased from 8 to 2 days (p less than 0.001). The time to cessation of new lesions was decreased from a median of 2 days to 0 days (p less than 0.001). Intravenous acyclovir is an effective treatment in decreasing the length and severity of primary genital herpes. (Author abstract) (2 Refs)

111. DRUG-RESISTANT HERPES SIMPLEX VIRUS IN VITRO AND AFTER ACYCLOVIR TREATMENT IN AN IMMUNOCOMPROMISED PATIENT.

Schnipper LE, Crumpacker CS, Marlowe SI, Kowalsky P, Hershey BJ, Levin MJ
Div. Oncology, Beth Israel Hosp., 330 Brookline Ave., Boston, MA, 02215
Am J Med; 73(1A):387-392 1982

An acyclovir-resistant herpes simplex virus (HSV) has been isolated from an immunocompromised patient during treatment for severe orofacial HSV infections with acyclovir. The resistant virus is deficient in expression of the HSV thymidine kinase (TK). Emergence of acyclovir resistance during clinical use appears to parallel the in vitro observations of selection for TK-deficient, acyclovir-resistant viruses following serial passage in the presence of the drug. The clinical importance of drug-resistant HSV is unclear, and further investigations are required to determine whether it will be an impediment to successful therapy of HSV infections. (Author abstract) (18 Refs)

112. GENETIC MECHANISMS OF RESISTANCE OF ACYCLOVIR IN HERPES SIMPLEX VIRUS.

Crumpacker CS, Schnipper LE, Chartrand P, Knopf KW
Div. Infectious Disease, Beth Israel Hosp., Room L201, 330 Brookline Ave., Boston, MA, 02215
Am J Med; 73(1A):361-368 1982

Resistance to acyclovir in herpes simplex virus (HSV) is mediated by two genetic loci on the herpes virus genome: viral thymidine kinase and DNA polymerase. Passage of HSV in the presence of 10 uM or 2 uM acyclovir readily coselects for virus deficient in the expression of viral thymidine kinase and resistance to acyclovir. Other workers have shown that passage of HSV in serum-starved cells in the presence of acyclovir selects for a mutant virus possessing a thymidine kinase with an altered substrate specificity and inability to phosphorylate acyclovir. Mutants with temperature-sensitive lesions in the viral DNA polymerase loci of HSV also exhibit resistance to antiviral drug phosphonoacetic acid (PAA) and acyclovir. The mutations conferring resistance to PAA and acyclovir are closely linked within the DNA polymerase locus. The map limits containing mutations that confer resistance to PAA and acyclovir are found within a 1.3 kilobase pair (kbp) region of DNA sequences in HSV-2 (map unit 40.2 to 41.0) and within a 2.6 kbp region of DNA sequence in HSV-1 (map units 40.2 to 41.8). The DNA polymerase loci of HSV also contains a region of DNA sequences to the left of the region defining the resistance mutation which determines the type specific sensitivity of HSV-1 and HSV-2 to acyclovir. Two HSV-1/HSV-2 recombinants were selected for further analysis of resistance. Viral DNA polymerase enzymes were purified from the R6-26 and R6-34 recombinants; the resistant recombinant R6-34 was shown to process an altered viral DNA polymerase. This altered viral DNA polymerase exhibited resistance to three inhibitors of DNA polymerase activity, PAA, acyclovir-TP, and 2'3'dideoxynucleotide triphosphate (didNTPs). The polymerase from R6-34 and the resistant parent possess a much higher Ki for the PAA and the didNTP than do the sensitive strains. A 1.3 kbp region of HSV-1 DNA within the DNA polymerase locus contains resistance mutations to three DNA polymerase inhibitors, codes for an amino acid sequence of 42,000 mol wt, and defines an active center of the HSV DNA polymerase enzymes. (Author abstract) (32 Refs)

113. ACYCLOVIR TREATMENT OF HERPES VIRUS INFECTIONS IN IMMUNOCOMPROMISED HUMANS. AN OVERVIEW.

Alford CA

Univ. Alabama Medical Center, Room 609 CDLD Building, Birmingham, AL, 35233

Am J Med; 73(1A):225-228 1982

As reflected in the preclinical and early clinical data, acyclovir seems destined to have a very useful role in the treatment and/or prophylaxis of herpes virus (HSV) infections in immunosuppressed humans. If the preclinical predictions can be extrapolated to varicella-zoster (V-Z) infections, acyclovir could well also play a meaningful role in therapy of V-Z infections in the immunosuppressed host; however, this conjecture awaits proof by controlled studies in humans. Clearly the usefulness of acyclovir for treatment of V-Z infections should be compared with that of adenine arabinoside (ara-A) to put into proper perspective the relative efficacies of the two drugs for future therapeutic regimens. The need for comparative studies is most important at this early stage of antiviral drug development, to avoid ethical problems that will cloud the knowledge needed to move forward in a positive way. In any event, the development of acyclovir, with its targeted approach, represents a real fundamental advance in antiviral drug development. Together with the development and deployment of ara-A, it should provide the needed impetus for a surge in the creation of new antiviral compounds for tomorrow. (Author abstract) (12 Refs)

114. MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTIONS IN IMMUNOCOMPROMISED PATIENTS. A MODEL FOR EVALUATION OF TOPICAL ANTIVIRAL AGENTS.

Whitley R, Barton N, Collins E, Whelchel J, Diethelm AG

Room 609 CDLD Building, Box 313, University Station, Birmingham, AL, 35294

Am J Med; 73(1A):236-240 1982

Forty-three immunocompromised patients with progressive cutaneous herpes simplex virus infections were studied in a double-blind, placebo-controlled evaluation of topically applied acyclovir. Patients were randomized and 22 received acyclovir and 21 placebo; medications were applied four times daily for 10 days. Both study populations were balanced for all demographic characteristics. Acyclovir therapy resulted in no median differences in time to total healing compared with placebo responses, p = 0.13. However, those patients who received the acyclovir ceased shedding virus more rapidly, p less than 0.001, and lost pain more readily, p = 0.04, than placebo counterparts. Neither group experienced adverse effects. Because of the protracted nature of mucocutaneous herpes simplex infections in these patients, the immunocompromised host provides a good model for evaluation of topical antiviral therapy. (Author abstract) (18 Refs)

115. ACYCLOVIR IN IMMUNOCOMPROMISED PATIENTS WITH CYTOMEGALOVIRUS DISEASE. A CONTROLLED TRIAL AT ONE INSTITUTION.

Balfour HH, Bean B, Mitchell CD, Sachs GW, Boen JR, Edelman CK

Univ. Minnesota Health Sciences Center, Box 437 Mayo Building, Minneapolis, MN, 55455

Am J Med; 73(1A):241-248 1982

Nine of 16 immunocompromised patients with laboratory-documented cytomegalovirus (CMV) disease were given intravenous acyclovir in a randomized, placebo-controlled, double-blind treatment study. Fifteen of the 16 patients were organ transplant recipients, 11 of whom had a renal allograft. Patients given acyclovir (500 mg/m2 3x daily for 7 days) experienced no major side effects. Acyclovir recipients had a significantly faster rate of improvement (p = 0.0437, Breslow test; p = 0.0595, Mantel-Cox), and a more rapid rate of defervescence (p = 0.0338, Breslow test; p = 0.0208, Mantel-Cox). The median day of improvement was 7 for the acyclovir recipients, and at least 31 for the placebo recipients. The median day afebrile was 13 for the acyclovir group and at least 31 for the placebo group. Three of the nine acyclovir recipients died, two of whom were semicomatose and septic with Bacteroides fragilis before the first dose of acyclovir was given. Four of the seven placebo recipients died. Although CMV could be recovered from throat and urine of acyclovir recipients throughout the study, viremia ceased after the 1st day of drug infusion. We conclude that acyclovir may be useful for treatment of CMV disease in certain immunosuppressed patients especially renal allograft recipients. Because the clinical response to acyclovir was not uniform and the number of patients studied was small, we are conducting another larger controlled trial of acyclovir for febrile renal transplant patients with CMV infections to extend and clarify the results of the first study. Patients randomized to acyclovir will receive 500 mg/m2 3x daily for 2 wk. The protocol includes in vitro testing of patients' CMV isolates for susceptibility to acyclovir and monitoring plasma concentrations of the drug. (Author abstract) (30 Refs)

116. PHARMACOKINETICS OF ACYCLOVIR IN HUMANS FOLLOWING INTRAVENOUS ADMINISTRATION. A MODEL FOR THE DEVELOPMENT OF PARENTERAL ANTIVIRALS.

Whitley RJ, Blum MR, Barton N, De Miranda P
Univ. Alabama in Birmingham, CDLD Building, Room 609, Box 313, Univ. Station, Birmingham, AL, 35294
Am J Med; 73(1A):165-171 1982

Data are reported from three step-wise pharmacokinetic studies in 43 patients who received acylcovir. Dosage regimens began at 0.5 mg/kg administered as a single dose intravenously and were increased to 15 mg/kg per dose given 3x daily for 5 days. All patients evaluated were immunocompromised by underlying disease or received cytolytic and/or cytotoxic therapy. Patients with virologically confirmed herpes simplex or zoster infections were assessed in the multiday, multidose pharmacokinetic trial. Postinfusion plasma concentrations of acyclovir declined in a biphasic manner such that the plasma-concentration time data were fitted by a two-compartment, open-model with zero-order input. The drug's half-life showed little variation with a mean of 3.16 +-0.20 hr. In both single-dose and multiple-dose studies there was dose proportionality with peak plasma levels and area under the plasma concentration-time curve indicating dose-independent pharmacokinetics. The kidney was the principal route of drug clearance with a mean recovery of 60 +-12%. Renal clearance exceeded creatinine clearance indicating renal tubular secretion of drug. No significant clinical or laboratory evidence of toxicity appeared. These studies provide a foundation for the evaluation of acyclovir in controlled trials. (Author abstract) (20 Refs)

117. TREATMENT OF LIFE-THREATENING EPSTEIN-BARR VIRUS INFECTIONS WITH ACYCLOVIR.

Sullivan JL, Byron KS, Brewster FE, Sakamoto K, Shaw JE, Pagano JS
Dept. Pediatrics, Univ. Massachusetts Medical Center, 55 Lake Ave. North, Worcester, MA, 01605
Am J Med; 73(1A):262-266 1982

Two pediatric patients with life-threatening Epstein-Barr virus infections were studied immunologically and treated with acyclovir [9-(2-hydroxyethoxymethyl) guanine]. The patient with chronic active Epstein-Barr virus infection who experienced massive hepatosplenomegaly, pancytopenia, and failure to thrive demonstrated abnormalities of T and B lymphocytes. A second patient, with X-linked lymphoproliferative syndrome, experienced a rapidly fatal course of acute Epstein-Barr virus infection which typifies this yet undefined immunodeficiency to Epstein-Barr virus. In each case, objective evidence for clinical improvement or antiviral effect of acyclovir treatment was not apparent. Abnormally productive Epstein-Barr virus infections did not appear to play a major role in the clinical syndromes observed. Current studies are focused on treatment of immunologically normal patients with early complicated Epstein-barr virus infection. (Author abstract) (23 Refs)

118. TREATMENT OF HERPES VIRUS INFECTIONS IN IMMUNOCOMPROMISED PATIENTS WITH ACYCLOVIR BY CONTINUOUS INTRAVENOUS INFUSION.

Spector SA, Hintz M, Wyborny C, Connor JD, Keeney RE, Liao S (c/o Connor) Dept. Pediatrics, M-009, Univ. California at San Diego, La Jolla, CA, 92093
Am J Med; 73(1A):275-280 1982

Sixteen immunocompromised patients with herpes virus infections were treated for 3 to 5 days with continuously administered intravenous acyclovir. Patients received initial acyclovir infusions over 5 min in dosages ranging from 1.5 to 5.0 mg/kg followed by continuously infused acyclovir at 7.2, 14.4, 21.6, 28.8, 36.0, or 43.2 mg/kg per day. The mean serum plateau levels of acyclovir determined by radioimmunoassay ranged from 4.1 uM for the 7.2 mg/kg per day dosage to 36.6 uM for the 43.2 mg/kg per day dose. A mean of 75% of acyclovir administered was recovered in the urine of patients treated. Eleven of 13 patients with varicella-zoster virus (VZV) infections had no new vesicle formation after 3 days of acyclovir treatment and all patients ceased to have new vesicles after 5 days of therapy. For the nine patients from whom complete viral cultures were available, six ceased to shed virus at 3 days, and viral shedding ceased by 5 days in all patients treated with acyclovir. No clinical or laboratory adverse reactions were associated with acyclovir therapy. These data suggest that acyclovir given by continuous intravenous infusion may be useful in the treatment of herpes virus infections in immunocompromised patients. (Author abstract) (11 Refs)

119. DOUBLE-BLIND CONTROLLED TRIAL OF TOPICAL ACYCLOVIR IN GENITAL HERPES SIMPLEX VIRUS INFECTIONS.

Corey L, Benedetti JK, Critchlow CW, Remington MR, Winter CA, Fahnlander AL, Smith K, Salter DL, Keeney RE, Davis LG, Hintz MA, Connor JD, Holmes KK
Virology Lab., Children's Orthopedic Hosp. Medical Center, P.O. Box C5371, Seattle, WA, 98105
Am J Med; 73(1A):326-334 1982

Sixty-nine patients with first episodes and 111 with recurrent episodes of genital herpes simplex virus (HSV) infection were enrolled in a double-blind trial comparing a 5% topical acyclovir ointment vs placebo, polyethylene glycol (PEG). Among acyclovir recipients with first episodes of genital herpes, the mean duration of viral shedding from genital lesions, 2.0 days, mean duration of local pain or itching, 3.6 days, and mean time to healing of lesions, 11.2 days, were less than in placebo recipients, 4.6, 6.7, and 15.8 days, respectively (p less than 0.05 for each comparison). Among patients with recurrent genital herpes, the mean duration of viral shedding from genital lesions was 0.8 days in acyclovir recipients compared with 1.7 days in placebo recipients (p less than 0.001). Among men with recurrent genital herpes, the mean time to crusting and healing of lesions was 3.5 and 7.6 days in acyclovir recipients compared with 5.0 and 9.7 days in placebo recipients, p = 0.03 and 0.07, respectively. No significant differences in the duration of symptoms or healing times were noted between acyclovir- and placebo-treated women with recurrent genital herpes. Acyclovir therapy was not associated with a decrease in frequency of clinical recurrences or an increase in the time to the next recurrence in patients with either first or recurrent genital herpes. Topical acyclovir appears effective in shortening some of the clinical manifestations of genital HSV infections. (Author abstract) (18 Refs)

120. MULTICENTER COLLABORATIVE TRIAL OF INTRAVENOUS ACYCLOVIR FOR TREATMENT OF MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTION IN THE IMMUNOCOMPROMISED HOST.

Meyers JD, Wade JC, Mitchell CD, Saral R, Lietman PS, Durack DT, Levin MJ, Segreti AC, Balfour HH
Program in Infectious Diseases, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Am J Med; 73(1A):229-235 1982

Intravenous acyclovir was evaluated in the treatment of 97 immunocompromised patients with mucocutaneous herpes simplex virus infection in a randomized, double-blind, placebo-controlled trial. Acyclovir recipients had significantly shorter periods of virus shedding (p less than 0.0002) and lesion pain (p less than 0.01), and more rapid lesion scabbing (p less than 0.004) and lesion healing (p less than 0.04). The most common adverse reaction was a low incidence of peripheral vein irritation; no serious toxicity could be definitely attributed to acyclovir treatment even in these seriously ill patients. Intravenous acyclovir offers both safe and effective treatment for mucocutaneous herpes simplex virus infection in the immunocompromised host. (Author abstract) (36 Refs)

121. CONTROLLED TRIAL OF ORAL ACYCLOVIR IN THE THERAPY OF RECURRENT HERPES SIMPLEX GENITALIS. A PRELIMINARY REPORT.

Reichman RC, Ginsberg M, Barrett-Connor E, Wyborny C, Connor JD, Redfield D, Savoia MC, Richman DD, Oxman MN, Dandliker PS, Badger GJ, Ashikaga T, Dolin R
Infectious Diseases Unit, Given Medical Building, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Am J Med; 73(1A):338-341 1982

A randomized, placebo-controlled, double-blind study was performed to evaluate the efficacy and toxicity of orally administered acyclovir in the treatment of patients with recurrent herpes simplex genitalis (HSG). A total of 107 patients from centers in Burlington, Vermont, and San Diego, California, were entered into the study within 48 hr of the onset of lesions. Patients who received acyclovir shed virus for 1.8 +-0.6 days (mean +- SEM) compared with 2.8 +-1.2 days for those who received placebo. The duration of shedding from genital lesions of patients in the acyclovir-treated group was significantly less than from lesions of patients who received placebo (p = 0.016 by a logrank test). An analysis of the toxicity of the drug was performed in 52 of the study participants. Acyclovir was well-tolerated and no alterations were observed in measurements of bone marrow, liver, or kidney function. Orally administered acyclovir is a promising antiviral compound for the treatment of recurrent HSG. (Author abstract) (16 Refs)

122. PATIENT-INITIATED THERAPY FOR RECURRENT GENITAL HERPETIC INFECTIONS.

Nahmias A, Kerrick G, Keyserling HL, Davis G, Alexander J, Corey L, Hatcher V, Luby J, Mills J, Sacks S
Div. Infectious Diseases, Allergy, and Immunology, Emory Univ. Sch. Medicine, Atlanta, GA, 30335
Am J Med; 73(1A):342-346 1982

Therapy for recurrent genital herpes is difficult to evaluate because of the short duration of lesions and viral shedding. Very early treatment, however, can be begun by patients who experience prodromes before onset of lesions. We have found prodromes to occur in 73% of male and 84% of female patients; 57% of the men and 68% of the women experienced prodromes in at least three out of every four recurrent episodes. Variables that might affect results of such a patient-initiated study evaluating topical acyclovir included: application of the ointment (drug or placebo) without prodrome (10%); the possibility of a false prodrome (less than or equal to 10%); long intervals between experiencing a prodrome and ointment application (15% greater than 24 hr); the inability to sense a prodrome during sleep; lack of ointment application to the involved areas with initial or later lesions (approximately 15%); noncompliance of enrollees in returning for study evaluations (greater than or equal to 10%). Such variables will need to be considered when the code is broken in this multicenter study, as well as for patient-initiated studies with other formulations of acyclovir or with other drugs. Earlier negative studies with other agents given within 2 to 3 days of appearance of lesions might also require reevaluation with similar patient-initiated studies. (Author abstract) (4 Refs)

123. RECENT AND FUTURE DEVELOPMENTS IN ANTIVIRAL CHEMOTHERAPY.

Prusoff WH, Chen MS, Lee JJ, Lin TS, Mancini WR, Otto MJ, Spivack J

Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510

Excerpta Med Int Congr Ser; 571:428-436 1982

Recent developments in clinically effective antiviral drugs are reviewed. Since toxicity in the uninfected cell is a major problem, attention should be given to drugs that are not active in the uninfected cell, but have activity in the infected cell. A discussion is presented of: (I) enzymes that catalyze reactions unique to the virus infected cell, and are also essential for viral replication, and (II) enzymes which are sufficiently different from their host cell counterparts, so that selective intervention may be possible. Further study of the antiviral state produced by interferon may result in important future developments. Other developments looking more into the future may involve selective binding, which evolves from studies which indicate formation and regulation of the herpes simplex virus-proteins alpha, beta, and gamma in a sequential and interdependent manner. Other approaches involve selective hybridization of inhibitory polynucleotides that are design based on the identification of unique sequences of viral messenger-RNA. Other approaches involve use of selective penetration, 'suicidal activation', temperature-sensitive liposomes, and magnetically responsive albumin microspheres for delivery of drugs. The problem of latency must be attacked. The most important development of recent years is the knowledge that antiviral drugs can be formulated based on a qualitative difference created specifically by the virus. (30 Refs)

124. CHEMISTRY AND POTENT ANTIVIRAL ACTIVITY OF 2'-FLUORO-5-SUBSTITUTED-ARABINOSYL-PYRIMIDINE NUCLEOSIDES.

Fox JJ, Watanabe KA, Lopez C, Philips FS, Leyland-Jones B

Sloan-Kettering Inst. for Cancer Res., 145 Boston Post Road, Rye, NY, 10580

Excerpta Med Int Congr Ser; 571:135-147 1982

The chemical synthesis and some experimental and clinical studies on the antiviral activity of a number of 2'-fluoro-5-substituted-arabinosyl-pyrimidine nucleosides are presented. 2-Fluoro-5-iodo-ara-cytidine (FIAC) is effective against herpes simplex virus (HSV) Type 1 and 2 and is less toxic than other antiherpes compounds currently in use. This selective activity depends in part on the virus-specified thymidine kinase. While FIAC structurally is an analogue of ara-C (1-beta-arabinofuranosylcytosine), it is not reversed by deoxycytidine. Various in vitro and in vivo studies on FIAC and 2-fluoro-5-methyl-ara-uridine (FMAU) indicate their utility against HSV-1 infections. Clinical studies with FIAC are reviewed. Dose-limiting toxicity is hematopoietic. A randomized double-blind Phase II trial has been initiated to test the antiviral efficacy of FIAC compared to arabinosyladenine in immunosuppressed patients with serious viral infections (herpes zoster virus and HSV). Two other trials have been initiated in a bone marrow population. Early clinical trials with FIAC are most encouraging. (29 Refs)

125. IN VITRO BIOLOGICAL ACTIVITY OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE AND THE BIOCHEMICAL ACTIONS OF ITS TRIPHOSPHATE ON DNA POLYMERASES AND RIBONUCLEOTIDE REDUCTASE FROM HELA CELLS.

Tseng WC, Derse D, Cheng YC, Brockman RW, Bennett LL

(c/o Cheng) Dept. Pharmacology, Univ. North Carolina Sch. Medicine, 917 Faculty Laboratory Office Building 231H, Chapel Hill, NC, 27514

Mol Pharmacol; 21(2):474-477 1982

Suitability of 9-beta-D-arabinofuranosyl-2-fluoroadenine (2-F-araA) as a substrate for cytoplasmic deoxycytidine (dCyd) kinase and for mitochondrial pyrimidine deoxynucleoside (dPyd) kinase was examined utilizing highly purified enzymes from human leukemic blast (HeLa) cells. 2-F-araA was inhibitory to the growth of HeLa cells in culture and the concentration for a 50% inhibition (I50) was 0.25 uM. The drug was less effective against the replication of herpes simplex virus Type 1 and 2 and was inhibitory only at concentrations that were toxic to host cells (5 uM). As compared with dCyd at a concentration of 0.4 milliM (mM), 2-F-araA (0.4 mM) was a good substrate for the cytoplasmic dCyd kinase but was a poor substrate for the mitochondrial dPyd kinase. At identical deoxynucleoside triphosphate concentrations, the 5'-triphosphate of 2-F-araA (2-F-araATP) was much more inhibitory to DNA alpha-polymerase than to beta-polymerase. 2-F-araATP strongly inhibited ADP reductase and cytidine diphosphate reductase activities with I50 values of 1 uM and 8.5 uM, respectively. The inhibition by 2-F-araATP of DNA alpha-polymerase and ribonucleotide reductase suggested that 2-F-araATP may exert its action through a 'self-potentiation' mechanism by decreasing deoxyATP formation. (16 Refs)

126. E-5-(2-BROMOVINYL-2'-DEOXYURIDINE) (BVDU), PHARMACOLOGY AND CLINICAL EXPERIENCE.

Sim IS, Meredith DM, Nuttall J, McCullagh KG

Dept. Biology, Searle Res. and Development, Div. G. D. Searle and Co., Ltd., P.O. Box 53, Lane End Road, High Wycombe, Buckinghamshire HP12 4HL, England

Excerpta Med Int Congr Ser; 571:157-164 1982

Studies on the mechanism of action, and the efficacy in animal models and in humans of the antiviral compound E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) are presented. Various studies indicate that the selectivity of BVDU for herpes simplex virus (HSV) Type 1 compared with HSV2 resides primarily at the level of the interaction with thymidine kinase. BVDU is effective in the treatment of HSV1 infections in many animal model systems after either topical or systemic application. Metabolic studies show that BVDU is well absorbed from the gastrointestinal tract of rats, mice, monkey and man. BVDU is effective in the treatment of HSV infections in humans and in the systemic treatment of herpes zoster (HZ). In an uncontrolled study reported in four cancer patients with severe localized or disseminated HZ, BVDU (7.5 mg/kg/day, po x 5 days) gave encouraging results. No new lesions developed during BVDU therapy and existing lesions healed briskly. In patients with disseminated HZ, there was dramatic improvement in their condition with fever resolving with 24 hr of start of BVDU therapy. (16 Refs)

127. DIFFERENTIAL PHOSPHORYLATION OF (E)-5-(2-BROMOVINYL)-2'-DEOXYURIDINE MONOPHOSPHATE BY THYMIDYLATE KINASES FROM HERPES SIMPLEX VIRUSES TYPES 1 AND 2 AND VARICELLA ZOSTER VIRUS.

Fyfe JA

Wellcome Res. Laboratories, Research Triangle Park, NC, 27709

Mol Pharmacol; 21(2):432-437 1982

Influence of virus-coded thymidylate (dTMP) kinases on the antiviral effectiveness of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BrVdUrd) was studied. The 5'-monophosphate of BrVdUrd (BrVdUMP) was phosphorylated in reaction mixtures with either cytosol extracts or with purified virus-associated dTMP kinases from cells infected with herpes simplex virus Type I (HS-I). No phosphorylation was detected with the corresponding catalysts from herpes simplex virus Type II (HS-II) or from host cells. The amount of extractable dTMP kinase was approx 50-fold that extractable from HS-II virus-infected cells. The dTMP kinase from HS-I virus phosphorylated BrVdUMP at 9% the rate of dTMP phosphorylation as compared with less than 0.2% for the enzyme from HS-II virus. The inefficient phosphorylation of BrVdUMP with HS-II virus correlated well with the observation that replication of HS-I virus is 100-fold more sensitive to BrVdUrd than is that of HS-II virus and suggests a cause-and-effect relationship. The maximal rates of of phosphorylation of BrVdUrd by the virus-coded deoxythymidine kinase and the amount of extractable enzyme were greater for cells infected with HS-II virus than for HS-I virus. Thus, the rate of BrVdUMP formation may be even greater with HS-II virus infection than with HS-I virus infection at concentrations of BrVdUrd attainable with treatment. (22 Refs)

128. ANTIHERPETIC CHEMOTHERAPY IN CHINA.

Chen HS, Tien PY

Inst. Antibiotics, Tian-Tan Beijing, People's Republic of China

Excerpta Med Int Congr Ser; 571:183-191 1982

A discussion is presented of in vitro, in vivo and clinical studies of various antiherpetic agents: 5-iodo-2'-deoxyuridine (IDU), 1-beta-D-arabinofuranoysylcytosine (ara-C), 9beta-D-arabinofuranosyladenine (ara-A), 2-2'-cyclocytidine (CC), 2-2'cyclocytidine-5'-monophosphate (CCMP), acycloguanosine (ACV), phosphonoacetate, phosphonoformate, polyinosinic acid:polycytidylic acid, and tilorone. In vitro studies were performed in PRK, HEK or human diploid cells against herpes simplex virus (HSV) I and II. Electron microscopic studies are presented of drug-treated HSV-infected cells in tissue culture. In vivo studies are reported on herpes keratitis in rabbits, herpes encephalitis in mice, herpes cutaneous infection in guinea pigs, and herpes vaginitis in mice. In clinical trials with herpes keratitis in a number of hospitals, IDU and ara-A were effective and are now in regular clinical use; ara-C, while effective, showed a toxic effects on the cornea and prolonged healing. Topical 0.5% CCMP in 21 cases of different types of herpes keratitis showed good therapeutic effect compared to CC. Topical ACV shows promise in the treatment of HSV keratitis. Poly I:C treatment of patients with herpes zoster (1-2 mg 2x/wk, sc) led to a significant shortening of disease; there were no severe side effects, except a few cases of transient low grade fever. Recurrence of disease and development of drug resistance are continuing problems. (20 Refs)

129. DIFFERENT IN VITRO EFFECTS OF DUAL COMBINATIONS OF ANTI-HERPES SIMPLEX VIRUS COMPOUNDS.

Schinazi RF, Nahmias AJ
Dept. Pediatrics, Div. Infectious Diseases, Allergy and Immunology, Emory Univ. Sch. Medicine, 69 Butler St., S.E., Atlanta, GA, 30335
Am J Med; 73(1A):40-48 1982

Five promising antivirals have been tested individually and in pairs on herpes simplex virus (HSV) Types 1 (Strain F) and 2 (Strain G) in Vero cells. These are: 9-(2-hydroxyethoxymethyl)guanine (acyclovir, ACV), 9-beta-D-arabinofuranosyladenine (ara-A), 5-trifluorothymidine (TFT), E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), and phosphonoformate (PFA). Various types of interactions depending on virus type were observed: synergistic [ara-A/TFT; ara-A/BVDU (G); BVDU/PFA (F)]; additive [ACV/ara-A; ACV/TFT; ACV/BVDU; ACV/PFA (G); BVDU/TFT; PFA/ara-A; PFA/TFT]; and sub-additive [ACV/PFA (F); ara-A/BVDU (F) and BVDU/PFA (G)]. Neither antagonism nor interference was noted for any combinations. (Author abstract) (35 Refs)

130. TREATMENT OF NASOPHARYNGEAL (NPC) CARCINOMA WITH INTERFERON: EPSTEIN-BARR VIRUS (EBV) SEROLOGY AND CLINICAL RESULTS OF A PILOT STUDY (MEETING ABSTRACT).

Connors JM, Andiman WA, Merigan TC, Savage ME, Liu E, Jacobs C
Stanford University School of Medicine, Stanford, CA, 94305
Proc Am Soc Clin Oncol; 1:C-771 1982

The purpose of this study was to determine the efficacy of human leukocyte interferon (alpha-IFN) in the treatment of NPC and its effect on IgA and IgG anti-EBV Viral Capsid Antigen (VCA), IgG and IgA Early Antigen (EAD), and oral excretion of EBV. Seven patients with recurrent NPC were studied. The mean age was 43 and the median performance status was 60. All patients had prior radiotherapy, and three patients had prior chemotherapy. Three had local/regional disease recurrence, and 4 had distant metastases. Alpha-IFN, was given at a dose of 10 X 10(6) units intramuscularly daily for 30 days. The mean IFN level 4-6 hours following injection was 190 units/ml (70-300 units/ml). The following anti-EBV serologic tests were monitored before, during, and after treatment: IgA-VCA, IgG-VCA, IgG-EAD and IgA-EAD. Titers ranged from 1:10-1:320 and did not change with treatment. Five patients were tested for oral excretion of EBV before and during IFN treatment. No patients excreted virus at any time. Treatment outcomes were as follows: 3 patients developed progressive disease after 22, 23 and 30 days of IFN; 3 had stable disease, but 2 of these did not complete a full course due to toxicity; 1 patient had a 90% reduction in tumor size of 1 month's duration. Toxicity included fatigue and fever in all patients, neutropenia in 1 patient. (no Refs)

131. EFFECTS OF HUMAN GAMMA INTERFERON ON CELL GROWTH, REPLICATION OF VIRUS AND INDUCTION OF 2'-5'-OLIGOADENYLATE SYNTHETASE IN THREE HUMAN LYMPHOBLASTOID CELL LINES AND K562 CELLS.

Tomita Y, Cantell K, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Int J Cancer; 30(2):161-165 1982

Human alpha interferon (IFN-alpha) and beta interferon (IFN-beta) showed antiviral and anticellular effects on human lymphoblastoid Daudi and P3HR-1 cells, but up to 1,000 units/ml of gamma interferon (IFN-gamma) showed no such effect. Though a fairly high level of dsRNA-dependent 2'-5'-oligoadenylate synthetase (2-5A synthetase) was found in Daudi cells, treatment of these cells with IFN-alpha and beta enhanced the enzyme level in cells at least four-fold, but IFN-gamma did not show any such effect. Lymphoblastoid Raji cells were insensitive to the antiviral and anticellular activities of IFN-alpha, beta and gamma, but 2-5A synthetase was induced in cells by the treatment with IFN-alpha and beta, though the enzyme level was lower than that found in interferon-treated Daudi cells. Human leukemic K562 cells were completely insensitive to IFN-alpha, beta and at the same time to IFN-gamma with regard to the antiviral, anticellular activities and to the induction of 2-5A synthetase. (Author abstract) (31 Refs)

132. BIOLOGIC CHARACTERIZATION OF A RECOMBINANT DNA HUMAN INTERFERON (MEETING ABSTRACT).

Kelsey DK, Kosak KM, Braaten BA, Glasgow LA
Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT
Pediatr Res; 16(4,part2):244A 1982

Recombinant DNA technology has resulted in the production of highly purified human interferon (HuIFN) preparations which are being evaluated as potential antiviral and antitumor agents in humans. We determined the biologic properties of a recombinant DNA interferon HuIFN alpha-2, in vitro and in vivo: (1) antiviral activity was documented by inhibition of CMV (cytomegalovirus), SFV, VSV (vesicular stomatitis-virus), HSV (Herpes simplex virus) 1 and 2 and vaccinia virus in WISH, human embryonic lung, foreskin fibroblast and osteosarcoma cells; (2) species specificity was indicated by a greater than 1000-fold reduction in anti-viral activity in murine cells in vitro; 3) immunomodulator activity was documented by augmentation of human NK cells and activation of human monocytes to be cytotoxic for human tumor cells; (4) antiproliferative activity was determined by inhibition of growth of human osteosarcoma cells (HOS) in vitro and prevention of growth of transplanted HOS tumors in athymic mice. In summary, HuIFN-2 was found to have antiviral, immunomodulatory, and antiproliferative activity characteristic of standard reference preparations of HuIFN. The feasibility of large scale production of pure preparations of HuIFN using recombinant DNA technology offers potential in the treatment of malignancies and viral infections of man. (no Refs)

133. EFFECT OF CYCLIC AMP AND CYCLIC GMP ON THE ACTIVITY OF INTERFERON AGAINST HERPES SIMPLEX VIRUS TYPES 1 AND 2, AND VESICULAR STOMATITIS VIRUS.

Stanwick TL, Nahmias AJ
Microbiology Dept., Univ. Health Sciences, Chicago Medical Sch., 3333 Green Bay Road, North Chicago, IL, 60064
Arch Virol; 72(4):247-256 1982

The antiviral action of interferon (IFN) on herpes simplex virus (HSV) Types 1 and 2, and vesicular stomatitis virus (VSV) was examined with respect to the intracellular levels of cyclic adenosine monophosphate (CAMP) and cyclic guanosine monophosphate (CGMP) in human fibroblast (HF) cultures. Interferon by itself increased the intracellular levels of CAMP, but had no effect on the CGMP levels. Inoculation of HF with HSV or VSV, however, decreased the CAMP levels.

Also, HSV inoculation elevated the CGMP levels, but VSV did not alter the CGMP levels. When HSV and IFN were added to the HF cultures in various combinations, HSV inhibited the IFN-induced elevation of CAMP and increased the CGMP levels to that characteristically observed with HSV inoculation in the absence of IFN. In contrast, IFN antagonized the VSV-associated decrease in CAMP levels. Although the yields of VSV were unaltered by the presence of CAMP- or CGMP-enhancing compounds, the yields of HSV were decreased with CAMP enhancers and increased with CGMP enhancers. The combination of IFN and CAMP enhancers had an additive effect in reducing the yields of HSV. Neither the CAMP or CGMP enhancers affected the action of IFN on VSV. These studies suggest that the interactions observed between HSV and cyclic nucleotides might account for the relatively refractive nature of HSV, as compared to VSV, toward the antiviral activity of IFN. (Author abstract) (23 Refs)

GENERAL REVIEWS

134. HERPES VIRUS. 1964-APRIL, 1982 (CITATIONS FROM THE NTIS DATA BASE).

National Technical Information Service
Natl. Technical Information Service, Springfield, VA
Gov Rep Announce Index (US); 82(17):3395 1982

The selected abstracts of research reports cover infectious diseases, blood transfusion, serodiagnosis, epidemiology, antigens and antibodies, antiviral agents and immunology as related to herpes virus. (This updated bibliography contains 182 citations, 8 of which are new entries to the previous edition). (Author abstract) (no Refs)

135. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART B.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

DNA repair technology is reviewed with emphasis on application for research and development purposes. Measurement of DNA repair synthesis by autoradiography, equilibrium sedimentation, photolysis of bromouracil, benzoylated naphthoylated diethylaminoethyl cellulose, and metabolic inhibitors is described. DNA strand breaks can be measured by sedimentation in alkaline sucrose gradients, alkaline elution, alkaline denaturation and hydroxyapatite chromatography, electron microscopy, gel electrophoresis, end labeling, and nitrocellulose membrane filtration. DNA daughter strand repair can be measured by postreplication repair in prokaryotes and mammalian cells, alkaline elution, and bromouracil photolysis. Biological parameters of DNA repair are discussed with respect to measurement of colony-forming ability and mutagenesis in diploid human cells and Chinese hamster cells; genetic markers for mutagenesis studies in mammalian cells; screening of mutagens by inhibition of DNA synthesis; measurement of sister chromatid exchange in mammalian cells; and purification, plaque assay, and inactivation of human adenoviruses 2 and 5. (491 Refs)

OTHER RELATED STUDIES

136. CLINICAL APPROACH TO INFECTION IN THE COMPROMISED HOST.

Rubin RH, Young LS
Infectious Disease and Transplantation Units, Massachusetts General Hosp., Boston, MA, 02115
Clinical Approach to Infection in the Compromised Host. New York, Plenum Medical Book Company, 653 pp., 1981.

A practical guide to patient management in the immunosuppressed host based upon available firm scientific data and on art and judgement of medicine when such data was unavailable is presented. The infections themselves, the potential therapeutic modalities, the clinical settings in which they occur, and the occurrence of such infections are discussed. Epidemiology and prevention of infection in the compromised host (CH), defects in host defense mechanisms, fever and septicemia, etiology and management of the compromised patient with fever and pulmonary infiltrates, CNS infections, fungal infections, mycobacterial and nocardial infections, parasitic disease, Legionnaires' disease, viral hepatitis, and herpes group virus (including Epstein-Barr) infections in CH are discussed. Infections complicating congenital immunodeficiency syndromes, management of infections in leukemia and lymphoma, infection complicating bone marrow transplantation, infection in the renal transplant patient, and surgical aspectes of infection in the CH are described. The immunocompromised patient lacks one or more components of the antimicrobial defense system. Abnormal host disease may result either from disease or from attempts to eradicate disease. Disorders of cell-mediated immunity have long been associated with herpesvirus infection. Such infections may be primary or may result from reactivation of latent virus. (1966 Refs)

137. TUMOR MARKER EXPRESSION IN INTERVAL BREAST CARCINOMAS (MEETING ABSTRACT).

Halter SA, Dupont WD, Hartmann WH
Departments of Pathology and Preventive Medicine, Vanderbilt Medical School, Nashville, TN
Lab Invest; 46(1):33A 1982

American Cancer Society-National Institutes of Health Breast Cancer Detection and Demonstration Projects (BCDDP) screened women annually for breast cancer. Women with negative mammograms at initial screen who presented before the next screen with histologically proven breast cancer were labeled interval cases. Twenty-three interval cases observed at the Vanderbilt BCDDP were compared with 31 age-, parity-, and family history-matched controls whose cancers were detected at annual screen. The expressions of carcinoembryonic antigen (CEA) and the gp 52 antigen related to the mouse mammary tumor virus were studied using immunoperoxidase techniques. The average age of all patients was 52 years. Seventeen per cent of interval patients were nulliparous and 30 per cent had a family history of breast cancer. Seventy-eight per cent of interval cases had infiltrating ductal carcinomas compared with 54 per cent of controls. Tumor size averaged 1.9 cm in both groups. No significant difference was found in presence of fibrocystic disease or breast side involved. Interval cases had an average of seven positive lymph nodes compared with two in controls. The presence of calcium in the tumors was significantly different between the two groups. Carcinoma in situ was present in significantly more control tissues. Blocks were available from 17 interval breast cancer cases and 26 matched controls. Sixty-five per cent of interval cases expressed CEA compared with 57 per cent of controls. Only two interval cases expressed gp 52 compared with 11 controls. (no Refs)

138. CHROMOSOMAL BREAKAGE AND SISTER CHROMATID EXCHANGE IN PERIPHERAL BLOOD LYMPHOCYTES AND LYMPHOBLASTOID CELL LINES IN THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

Barnabei VM, Sakamoto K, Seeley JK, Purtilo DT
(c/o Purtilo) Dept. Pathology, Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105
Cancer Genet Cytogenet; 6(4):313-321 1982

The frequencies of chromosomal aberrations and sister chromatid exchange (SCE) were measured in lymphoblastoid cell lines (LCLs) and in phytohemagglutinin (PHA)- and pokeweed mitogen (PWM)-stimulated lymphocytes from males with the x-linked lymphoproliferative (XLP) syndrome, their obligate carrier mothers, and control subjects. We observed an increased frequency of chromosomal aberrations including increased polyploidy in LCLs derived from families with XLP with time in culture. The SCE rate in LCLs (mean of 3.89 SCEs per cell) was much lower than that in PHA- or PWM-stimulated lymphocytes: PWM-stimulated lymphocytes showed 9.58 SCEs per cell and PHA-stimulated cells had 11.38 SCEs per cell. A greater number of chromosomal gaps and breaks in the D-group chromosomes of LCLs of affected males and carrier females were identified compared to the number expected, based on chromosomal length and the number of aberrations seen in PHA-stimulated cell cultures. No differences in the frequency of SCEs or chromosomal aberrations were found in control subjects and affected males or carrier females in the peripheral lymphocytes stimulated by PHA. Phenotypes of XLP appear to arise from failure of immune responses to Epstein-Barr virus (EBV) and not from intrinsic chromosomal breakage or instability. (Author abstract) (18 Refs)

139. A NEW EPSTEIN-BARR VIRUS NEGATIVE BURKITT'S LYMPHOMA DERIVED CELL-LINE. I. ANALYSIS OF CELL SURFACE MARKERS AND ABNORMAL EXPRESSION OF HLA ANTIGENS.

Kalil J, Fellous M, Tanigaki N, Rosa F, Pagniez C, Herzog C, Dastot H, Lenoir G
(c/o Fellous) Immunogenetique Humaine, Institut Pasteur, 28, Rue de dr. Roux, F-75724 Paris Cedex 15, France
Tissue Antigens Histocompat Immunogenet; 20(1):47-62 1982

CHEV, a new Epstein-Barr virus negative Burkitt's lymphoma derived cell line has been studied. Karyotype analyses demonstrated the t (8; 14) characteristic translocation. Cell surface characterization of this line showed the presence of mu and chi immunoglobulin chains and beta2-microglobulin and the absence of the complement receptor. We are unable to detect HLA-A, B alloantigens on the cell surface which was in contrast with an apparently normal expression of these antigens in the cytoplasm. (Author abstract) (44 Refs)

140. EXPRESSION OF RECEPTORS FOR EPSTEIN-BARR VIRUS (EBV) ON LYMPHOID LEUKEMIC CELLS (MEETING ABSTRACT).

Vogler LB, Lenoir M, Flandrin G, Gerber P
Laboratories of Immunochem. and Immunopath. and Cytology, Hopital St. Louis, Paris, France
Pediatr Res; 16(4,part2):217A 1982

EBV has an unique affinity for human B lymphocytes. It is associated with infectious mononucleosis, African (endemic) Burkitt's lymphoma, nasopharyngeal carcinoma, and an x-linked lymphoproliferative (Duncan's) disease. To better understand the nature of EBV receptors on B cells, we examined receptor expression on lymphoid leukemic cells representative of discrete stages of lymphocyte differentiation, using an immunofluorescent method. Cells were incubated with EBV, then FITC-F(ab')2 fragments of human IgG anti-EBV membrane antigen. We conclude that EBV receptors appear very early, at the pre-B stage, in B cell development and that they are lost at or shortly before terminal differentiation to plasma cells. Non-endemic Burkitt's cells lacked receptors for EBV, suggesting an origin of this malignancy from an unique set or developmental stage of B lymphocytes. (no Refs)

141. APPLICATION OF A LIVE VARICELLA VACCINE IN CHILDREN WITH ACUTE LEUKEMIA.

Sakurai M, Ihara T, Ito M, Hirai S, Iwasa T, Oitani K, Kamiya H, Izawa T, Takahashi M

Dept. Pediatrics, Mie Univ., Sch. Medicine, Tsu-city, Mie-ken, Japan

Excerpta Med Int Congr Ser; 571:87-93 1982

Forty-three children with acute leukemia who were susceptible to herpes virus and who had been vaccinated with Takahashi's live attenuated varicella zoster virus, were followed closely for 6 yr. Patients were vaccinated usually 6 mo after complete remission, when the immunological status of the patient had returned to normal. Clinical manifestations (fever and/or rash) developed in seven children but were only serious in one patient. After exposure to natural varicella infection on 31 possible occasions, only one patient developed an infection. The occurrence of herpes zoster infection was not significantly different from that in children who had natural varicella infection before onset of leukemia. It is concluded that a live attenuated varicella virus vaccine can be used in leukemic children in remission, and provides a potent measure for preventing natural varicella infection. (5 Refs)

142. IN VITRO STUDY OF THE EFFECTS OF HUMAN LEUKOCYTE INTERFERON ON CELL DIVISION AND NATURAL KILLER CELL ACTIVITY.

Gorog G, Onody K, Toth M, Benczur M, Petranyi Gy, Beladi I, Hollan Zs

EGYT Gyogyszervegyeszeti Gyar, Budapest, Hungary

Orv Hetil; 123(24):1479-1482 1982

The in vitro study of the effects of different interferon preparations demonstrated considerable interindividual and interpreparation differences in the inhibition of mitogen-induced blast transformation of human peripheral lymphocytes and in the enhancement of the natural killer cell activity. The effects were, however, consistently dose-dependent when tested in several individuals. Positive correlation was found between the interferon-induced inhibition of thymidine uptake by tumor cell lines (Raji, Daudi, K-562) and the antiviral effect, which suggests the potential value of this method for the measurement of the interferon activity. (26 Refs) (In HUN)

143. SPONTANEOUS PRODUCTION OF ALPHA- AND BETA-INTERFERON IN HUMAN LYMPHOBLASTOID AND LYMPHOMA CELL LINES.

Adolf GR, Haas OA, Fischer P, Swetly P
Wrnst-Boehringer-Institut fur Arzneimittelforschung, Dr.-Boehringer-Gasse 5-11, A-1121 Wien, Austria
Arch Virol; 72(3):169-178 1982

A large number of human hematopoietic cell lines was examined for spontaneous production of interferon. Unconcentrated culture supernatants from 70 out of 71 B-lymphoblastoid cell lines contained considerable amounts of interferon (median titer 22 units per ml); a few lines produced more than 100 units/ml with peak values up to 500 units/ml. In contrast, only one B-lymphoma line out of 18 genuine lymphoma, myeloma, and leukemia cell lines tested spontaneously produced small amounts of interferon. Following treatment with 5-bromodeoxyuridine (BrdUrd), interferon was produced without further induction in most B-lymphoid cell lines, but not in any of the non-B, non-T, T-lymphoid or myeloid lines examined. Modulation of spontaneous interferon production by chemicals (sodium butyrate, dexamethasone, dimethylsulfoxide, a phorbol ester, and BrdUrd) was studied in more detail in three B-lymphoblastoid and four B-lymphoma cell lines. The patterns of responses observed were different for the action of different chemicals on a given cell line as well as between lymphoblastoid and lymphoma lines in general; furthermore, several lines of evidence suggest that chemicals can differentially influence spontaneous and virus-induced interferon production in a given cell line. The composition of spontaneously produced interferon was analyzed using antisera specific for HuIFN-alpha and HuIFN-beta. Interferons produced by untreated as well as BrdUrd-treated lymphoblastoid cells contained more than 95% IFN-alpha, whereas BrdUrd-treated lymphoma cells produced IFN-alpha as well as minor amounts (cell lines Namalwa and NC-37) or even over 90% of IFN-beta (Daudi). (Author abstract) (17 Refs)

144. CONTROL OF GROWTH OF A MALIGNANT LYMPHOID CELL LINE BY INTERFERON AND (2'-5') PA (MEETING ABSTRACT).

Leandersson T, Lundgren E, Nordfelth R
Laboratory for Cell and Tissue Culture Research, University of Umea, S-901 85 Umea, Sweden
Scand J Immunol; 15(1):136 1982

P3HR 1 is an EBV (Epstein-Barr Virus)-transformed Burkitt's lymphoma cell line, which has been shown to be IFN (interferon) sensitive. Upon IFN alpha addition the cell proceeds through the cell cycle and enters G0 after the first mitosis upon triggering by IFN. The rate of entry into G0 is dependent on the dose of IFN given. Dense cells differ in their cell cycle distribution compared to IFN-treated cells in that they seem to keep a normal cell cycle distribution as compared to exponentially growing cells. The levels of (2'-5') pA-synthetase was correlated to different growth states, and it was found that addition of (2'-5') pA core did not mimic the effect of IFN. (no Refs)

145. RETINOIC ACID SUPPRESSION OF HUMAN LEUKOCYTE INTERFERON PRODUCTION.

Abb J, Abb H, Deinhardt F

Max von Petterkofer-Instutute, Petterkoferstrasse 9A, 800 Munich 2, W. Germany

Immunopharmacology; 4(4):303-310 1982

The effect of retinoic acid (RA) on the production of interferon (IFN) by human peripheral blood leukocytes was investigated in vitro. Concomitant administration of RA and viral or nonviral IFN inducers to WBC cultures suppressed the production of IFN in a dose-dependent fashion. Max suppression of IFN yields were observed at an RA concentration of 15 ug/ml. A similar reduction in IFN yields was observed with RA added to sendai virus- or influenza virus-stimulated human lymphoblastoid cells. Incubation of WBC or lymphoblastoid cell lines (LCL) in the presence of 0.15% dimethylsulfoxide and IFN inducers had no significant effect on the basic production of antiviral activity. The inhibitory effect of RA on leukocyte IFN production in response to purified phytohemagglutinin (PHA-P) or influenza virus depended upon its near-concurrent addition to the cultures. Antiviral activity induced by treatment with PHA-P or concanavalin A was characterized as IFN-gamma. That induced by treatment with Corynebacterium parvum, viruses, polyinosinic-polycytidilic acid, or tumor cell lines shared properties with IFN-alpha. Addition of RA to WBC cultures markedly suppressed IFN yields in supernatants of human WBC incubated with lectin mitogens, bacterial products, viruses, polynucleotides, and lymphoblastoid tumor cells. The degree of suppression of IFN secretion by RA was similar with inducers of IFN-gamma and IFN-alpha. Implications of these findings for the use of retinoids for treatment of human cancer are discussed. (24 Refs)

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